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THE MEDICAL CLINICS
OF
NORTH AMERICA

Volume 6 Number 1

CLINIC OF DR. WILLIAM ENGELBACH

ST. JOHN'S HOSPITAL

ENDOCRINE ADIPOSITY

The Importance of Overweight as Compared with Loss of Weight. Fallacies of Etiology of Obesity. Rôle the Internal Secretions Play in Adiposity. I. Significance of Age Incidence, Grouping Overweight into (*a*) Infantile, (*b*) Juvenile, and (*c*) Adult Varieties. II. Diagnostic Evaluation of the Localization of Panniculus in Different Ductless Gland Disorders. Illustrated Descriptions of Classical Cases of (*a*) Thyroid, (*b*) Hypophyseal, (*c*) Gonad, and (*d*) Pluriglandular Adiposity. Treatment.

THE intent of this lecture is to demonstrate typical cases of adiposity due to disorder of the internal secretions, and to attempt to evaluate obesity as one of the most important diagnostic signs of ductless gland disorders. An apparently innocent, inexplicable gain in weight has never been given its relative importance as to its possible cause or the future health of its bearer. Loss of weight always has been taken to indicate some very serious abnormality, the cause of which is considered worthy of exhaustive investigation. On the other hand, gain in weight has always been heralded as a sign of unusual health, and has constantly been the reason for minimizing other very serious complexes with which it has been associated. In a great majority of cases the etiology of these many times serious and disabling obesities has been easily explained on the basis of habits, lack of exercise, increased food intake, excess of carbohydrates, family

idiosyncrasies, and other lay proof, which has frequently satisfied even the medical mind. Admitting that such causes—as diet, lack of exercise, etc.—do have some bearing upon certain cases, the fallacies of these deductions are soon proved by careful observation of a series of obese and emaciated patients. Furthermore, an attempt to overcome this over- or underweight affords very considerable additional information, negating the fact that the activity or the elimination of the individual has a great deal to do with the tendency to gain, lose, or maintain weight. The simple experiment of inquiring into the amount and kind of diet taken by a majority of obese individuals proves that, from the force of habit, acquired by many years of self-treatment, their intake actually is smaller and more deficient of carbohydrate foods than that of the individual of average weight. Their histories are a repetition of prolonged hygienic, hydrotherapeutic, and gymnastic efforts to reduce this weight. These efforts of diet, exercise, bathing, and "reduction cures," in the great majority of cases, have produced comparatively little effect. On the other hand, histories taken of the majority of cases of underweight and undernourishment show that their intake really is considerably excessive in caloric value, and that their activities are much below the average, without the consequent effect of producing an increase in nourishment, or even an inclination to obesity. These statements should be qualified by saying that reference is made only to those individuals who are absolutely free from general or systemic diseases other than those of the ductless glands, such as malignancy, infections, or any lesions retarding in any way the intake or assimilation of food through a decrease in appetite, structural, or chemical change. In other words, this discussion will be limited to those individuals who, after careful, prolonged diagnostic survey, have been found to be free from any disease or disorder except those primarily affecting the internal secretions, which might in any way either decrease or increase the weight, as compared with the height and age, above the normal.

Provided the above precepts can be accepted, we are then compelled to look for other causes for the unusual over- or under-

weight and disproportion due to the lack or overdeposition of adipose or other tissues present in these individuals. We must also concede that they are just as truly abnormal as are those having some well-known infection or malignancy. The causes of such abnormalities in the majority of cases must be in the katabolism, and not in the anabolism of the metabolism of the individual. In other words, it is not the amount of food consumed or the amount of exercise undertaken, but the amount of food, after it is properly anabolized, which is either stored in the body or broken down by katabolism, and excreted, which produces the balance in weight. It is just in this rôle of the regulation of the rate of metabolic activity that the internal secretions play their important part. The factor of overweight production corresponds closely to the metabolic rate, and can be measured by computing the pulmonic oxygen exchange in one of these glands, the thyroid. This metabolic rate, however, does not serve as a guide to the origin of the obesity in the uncomplicated disorder of the pituitary or gonads. For in these glandular deficiencies in which there is gradually progressive obesity repeated estimations of the metabolic rate show that it varies very little from the normal. In an attempt at solving these abnormalities studies of the blood fat are being made, with the hope that they will throw some additional light upon the etiology of the adiposities in the pituitary and gonad insufficiencies. While it is true that they must have some metabolic disturbance, it is the consensus of opinion of workers in this field that this is not evidenced in the oxygen exchange in the lung, and, for that reason, not related to the carbohydrate metabolism. This has led to the study of fat metabolism as a possible cause for these pituitary and gonad obesities. That they do occur is proved by clinical evidence. Observation of a large series of cases associated with these glandular disorders proves conclusively that there is a very classical and comparatively easily interpreted obesity specific for the hypophysis and gonads respectively.

The purport of this demonstration is to attempt to exhibit these adiposities typifying the under- or overweight occurring in classical endocrine disorders. The importance of this easily

recognizable sign in the early diagnosis of ductless gland disorder cannot be overestimated, and its interpretation refers as much to the relief and end-results in these cases, as it indicates the gland whose early disorder is so glaringly reflected upon the body surface of the patient. In fact, the recognition of this sign is so objective and conclusive as to make its diagnostic prominence and therapeutic indications probably of more value than any other one hormonic sign.

The basis for the following deductions regarding these endocrinous adiposities is the careful correlation of the studies made by Dr. John L. Tierney and the writer of 1995 cases of disorders of the ductless glands, as follows: thyroid, 609; pituitary, 285; gonad, 351; pluriglandular, 680; adrenal, 52; thymus, 14; pineal (?), 4.

It might be well at this place to reiterate our definition of an endocrine disorder as an endocrinous syndrome from which general or systemic disease or lesion has been excluded. As an illustration, these patients have undergone a complete diagnostic survey in order to determine whether a lesion or disease of any other system could be the primary cause for the endocrine complex; and if such a condition was demonstrable in the presence of a ductless gland disorder, the endocrine syndrome was always classified as a condition secondary to the other primary disease, and the case was not grouped with those having only primary disorders of the internal secretions.

The two great and simple aids, relative to the presence or absence of obesity, diagnostic of internal secretory disorder are: (I) *The age incidence at which the obesity occurs* and (II) *the localization and distribution of the adiposity.*

I. **The Age Incidence at Which the Obesity Occurs.**—The diagnostic value of the *age incidence* of the occurrence of the adiposity will be impressed upon anyone who will re-analyze groups of their case histories. The correlation of a large series of these cases, obtained from a review of their histories, has led us to group the adiposities according to age incidence into three divisions: (*a*) *Infantile adiposity*, (*b*) *juvenile adiposity*, and (*c*) *preadult* and *adult adiposity.*

(*a*) *Infantile Adiposity.*—We were first struck with the frequent recurrence of overweight at birth present in histories of cretins. Later, when we analyzed the histories of a considerable number of our adolescent hypothyroid females, we also found that a large percentage of these gave a history of having been overweight at birth. We have attempted to establish the arbitrary weight of $7\frac{1}{2}$ to 8 pounds as the maximum normal weight at birth in any infant otherwise apparently normal. It is taken for granted that monsters, hydrocephalus, and other objective abnormalities are to be excluded. If, in addition to this over-

Fig. 1.—Typical cretin at the ages of three, five, and sixteen. Note the classical facies at three, inability to walk at five, and absence of marked obesity at sixteen.

weight at birth, we obtained the chronologic first year history of late eruption of the first teeth (past seven months) and delayed walking and talking (later than one year), we have maintained that a diagnosis of hypothyroidism was tenable. It is emphatically proved, however, that there are no other demonstrable causes for the retardation in growth and development of the child during this first year of life. We do not mean to say that an otherwise unexplained overweight at birth is in itself sufficient upon which to base a diagnosis of hypothyroidism in an infant; yet we more than strongly urge that this sign in itself is very suggestive, and that, if followed by the other three se-

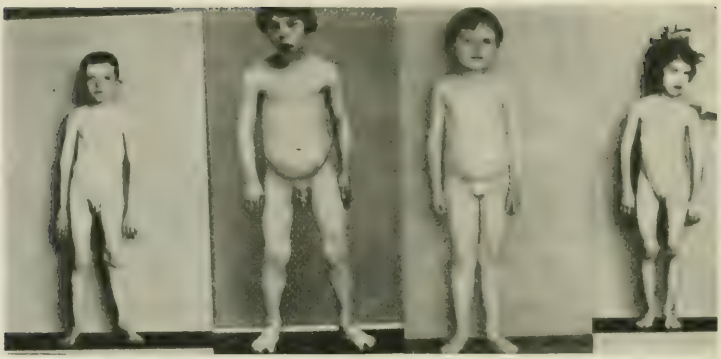

Fig. 2.—Four cretins varying in age from six to fourteen. Note the absence of obesity, also differences, depending upon involvement of other glands. The two at the extreme right and left are thyropituitary.

Fig. 3.—Typical thyropituitary girl, aged nine. From the age of one until six this case had the classical history and markings of the cretin, without obesity. Following the age of six typical girdle adiposity developed, furnishing a good illustration of insufficiency of the thyroid to which had been added insufficiency of the posterior lobe of the hypophysis.

quential cardinal signs late dentition, late locomotion, and delayed speech—the four taken together are sufficient, without other evidence of hypothyroidism, for placing the infant upon treatment for deficiency of the thyroid.

A perusal of the histories of these hypothyroid babies demonstrates further that they do not carry an excessive weight into their early childhood. In fact, the majority of them lose their overweight before they are two years of age. This possibly is due to the malnutrition induced by the difficult feeding and the susceptibility to infections characteristic of these infants. For these reasons children *after the age of three or four who have an adiposity probably are not hypothyroid*, or, if they are hypothyroid,

Fig. 4.—Supraclavicular fat pad in myxedema.

have added to this defect an insufficiency of the hypophysis, the description of which follows.

(*b*) *Juvenile Adiposity.*—Contrasted with the infantile adiposity occurring at birth we have an adiposity occurring in the juvenile age which is due to an entirely different ductless gland disorder—insufficiency of the posterior lobe of the pituitary gland. These adiposities most frequently begin between the age of five and the age of fourteen (or adolescence). The history in the great majority of these cases has shown that they were children who weighed less than 7 pounds at birth, and that they were free from the chronologic history of hypothyroidism presented in a preceding paragraph; that is, that the dentition, locomotion, talking, and weight, height, growth, and general

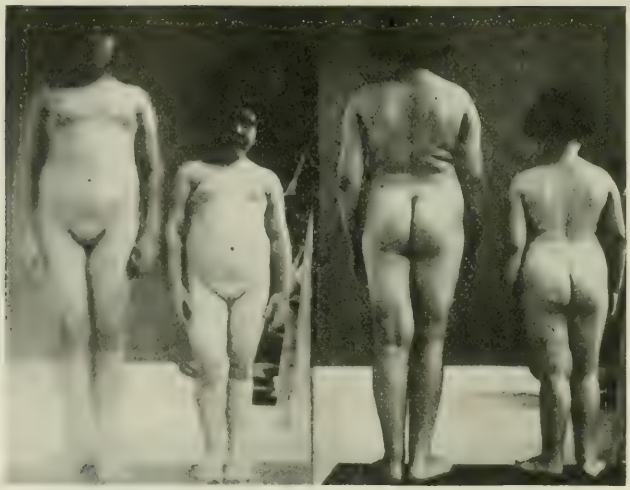

Fig. 5.—Classical hypopituitarism at the ages of six and ten. The mother was a classical bilobar hypopituitarism (Fröhlich's disease). Both of these cases were free from thyroid history, markings, or mental signs. Compare with Fig. 3, showing pituitary adiposity engrafted upon hypothyroidism.

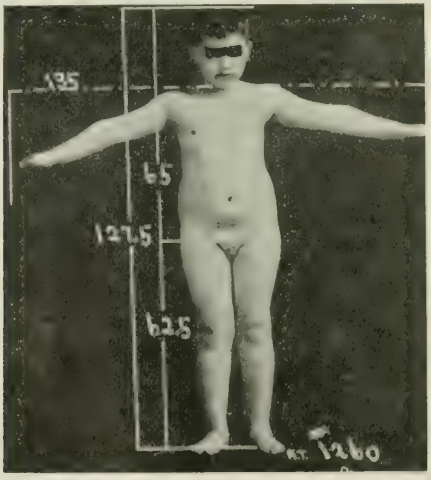

Fig. 6.—Hypopituitarism, seven years of age. Diagnosis was made upon the sudden increase in weight since the age of four and a half.

Fig. 7.—Hypopituitarism, aged seven. Weight, 120 pounds.

Fig. 8.—Hypopituitarism (bilobar), aged eleven. Onset of obesity occurred at nine. Note the small genitalia and the tendency to mammary and mons adiposity, indicating anterior lobe insufficiency even before the preadolescent age.

Fig. 9.—Typical bilobar hypopituitarism, aged fourteen. Note the classical adiposity and infantile genitalia.

Fig. 10.—Bilobar hypopituitarism, aged thirteen. Note the classical adiposity and aplasia of the genitals. (The mammary adiposity is more marked in these cases in which the anterior lobe is insufficient.)

development throughout were practically normal until the age of four or five. Between this age and adolescence they suddenly take on an unusual adiposity, which, within a few years, produced a disproportionate overweight, very noticeable without comparison with the standard height, age, and weight scale. There is no other appreciable abnormality associated with this obesity. In contrast to the hypothyroid child at this age *they do not have*

Fig. 11.—Classical hypopituitarism, bilobar, aged six, eleven, and eighteen. Note the absence of adiposity at the age of six and its presence at the age of eleven, whereas the typical Fröhlich's syndrome (bilobar insufficiency) is present at the age of eighteen. This well illustrates the diagnostic value of adiposity at the preadolescent age as indicative of hypophyseal insufficiency, although the function of the anterior lobe cannot be proved until after the adolescent age.

retardation in mental development. In fact, on the contrary, the majority of them are inclined to be precocious in mentality. Neither do they have the orthodontial or osseous changes, or any of the localized hormonic signs, such as the deep-set eyes, retrousse nose, thick lips, lordosis, pot-belly, umbilical hernia, and dermal and hair changes of the hypothyroid child. They contrast at this age with the hypogonad juvenile, who, as will be shown by the descriptions and figures (Figs. 13, 14, 19, 20),

has a tendency to emaciation, overgrowth of the long bones, and eunuchoid measurements, exactly opposite to the characteristics of this type of obesity. This juvenile adiposity is unquestionably an early and easily interpreted sign of what is frequently one of the most common and serious ductless gland disorders—insufficiency of the posterior lobe of the hypophysis. This obesity, however, is not confined to the juvenile age. Insufficiency of

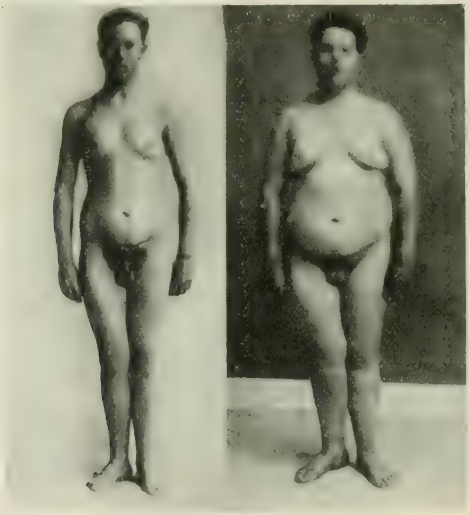

Fig. 12.—Bilobar hypopituitarism (aged fifteen) before (right) and after (left) treatment. Note the classical girdle, mammary adiposity, and aplasia of the genitalia. This adiposity of the mammæ, as well as the girdle, disappeared entirely, with the exception of a slight mons veneris shelving, following reaction to treatment. Notice the increased size of the genitals and growth of hair on the mons after treatment.

the posterior lobe of the pituitary occurring in the adult or preadult age, as will be shown in the following paragraph, produces the same classical adiposity. *The point to be emphasized*, however, is that *an adiposity occurring in the juvenile age* is nearly always *due to the insufficiency of the posterior lobe of the pituitary;* and the *age incidence* at which this adiposity occurs is, in the great majority of cases, *significant enough in itself to make a diagnosis* and to demand an immediate institution of treatment.

(*c*) *Adult Adiposity.*—As has been stated in the preliminary grouping of adiposities, those occurring in the adult or preadult age may be due to a disorder of the pituitary, the thyroid, or the gonads, or of a combination of these glands. The age incidence in these cases has only one significance, and that is relative to gonad adiposity. A careful review of the cases collected thus far has given us a great deal of confidence in the statement that adiposity due to *insufficiency of the gonads does not occur at birth, in the juvenile age, or in early adult life.* The one exception to this

Fig. 13.—Hypogonadism, aged nineteen. Note the absence of obesity (including the mammæ), except for slight fulness along the entire thigh, classical disproportion (lower measurement longer than upper, and span longer than height), and typical gonad facies.

rule is the trochanter adiposity localized over the trochanter area occurring in early castrates and classical eunuchs. The typical gonad adiposity will be described under the discussion of the localization and distribtion of the panniculus adiposis. As far as we are able to learn from our own material, this rarely occurs before the age of thirty-four or thirty-five. If this be true, the age incidence here again helps to exclude adiposity due to the generative organs; that is, one occurring before this age probably would be due to the pituitary, the thyroid, a pluri-

glandular syndrome, or possibly to other causes, but rarely, if ever, to insufficiency of the gonads. On the other hand, it is well known that pituitary adiposity, as well as thryoid adiposity, can occur much earlier or later in life than the third decade. The probabilities are that, in all those cases that occur after the age of thirty that have had a duration of more than a year or two, there is an involvement of more than one gland; and the later in life the adiposity occurs, the more certain it is that a

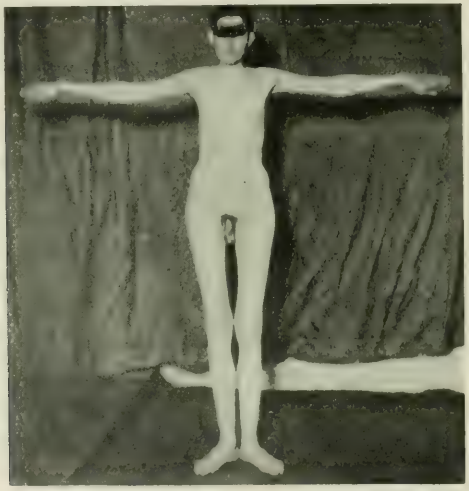

Fig. 14.—Hypogonadism, aged twenty-four. Note the absence of general and mammary adiposity, with the exception of an even fulness along the entire thigh. Proportions, facies, hands, etc., typical. (Courtesy of Dr. W. N. Adkins, Atlanta, Georgia.)

pluriglandular defect is present. The same statement holds true as to the duration of the adiposity in late adult life. The longer it has been present, the more liability there is that more than one gland has been involved, although it probably began as a uniglandular disorder.

The application of these deductions is pertinent to the prognosis. Because they relate in a general way to the physiologic activity of the individual ductless glands under discussion, the prognosis will depend upon the probability of physiologic reaction

or activation of these endocrine functions, and this, in turn, will depend upon the normal age epoch of their activity. Consequently, the later in life these various obesities occur, the worse must be the prognosis. The clinical application of the duration of the disease relative to the prognosis also has the most decided relation to the prognosis. The longer the duration, the more likelihood that more than one gland has become involved. The more glands that are defective in their physiologic function, the less is the probability that the patient will react to any treatment

Fig. 15.—Comparison of hypopituitary (left) with hypothyroid (right) of the same age (forty-one). Note the absence of cervical and dorsal padding and of extremity adiposity in the pituitary, and their presence in the thyroid.

which tends to substitute these secretions or stimulate their activity.

II. **Distribution of Adiposity.**—The second subdivision relative to the cause of adiposity and indicative of its diagnostic importance concerns the localization and distribution of the panniculus adiposis.

In a general way, (*a*) *thyroid adiposity* is so well-known and so well illustrated by the figures that it needs little reference. The usual dorsal hand padding, supraclavicular padding, and

evenly distributed universal adiposity of the thyroid were well described by William Gull (1873). A warning must be given, however, to those who depend upon the hand and cervical padding in infancy. It is very rare that it is objective enough during the first year upon which to place any dependence. Even in outspoken juvenile cretinism it is entirely absent except in a small percentage of cases (Fig. 16). Another hint that is valuable is that in positive cases this localized padding is frequently transient and evanescent. The adiposity in myxedema has been frequently mistaken for that due to the hypophysis. For this reason a number of contrasting cases are illustrated to bring out

Fig. 16.—Dorsal (hand) padding, rarely present in juvenile hypothyroidism.

the difference in the localization of these two forms of obesity (Figs. 15, 17, 18).

(*b*) *Pituitary adiposity* in childhood and adult life is located about the girdles. The hip and shoulder girdles both are involved. The pelvic girdle adiposity extends from the navel down to the juncture of the middle and lower thirds of the thigh. The shoulder girdle is less prominently affected, although in those cases in which there is a very decided pelvic girdle adiposity there usually is a closely demarcated shoulder obesity. This extends from the midclavicular region down to the insertion of the deltoid, and, in fact, is confined almost entirely to the deltoid

region, which localization might give it its name (deltoid adiposity). Besides these localized areas there usually is considerable

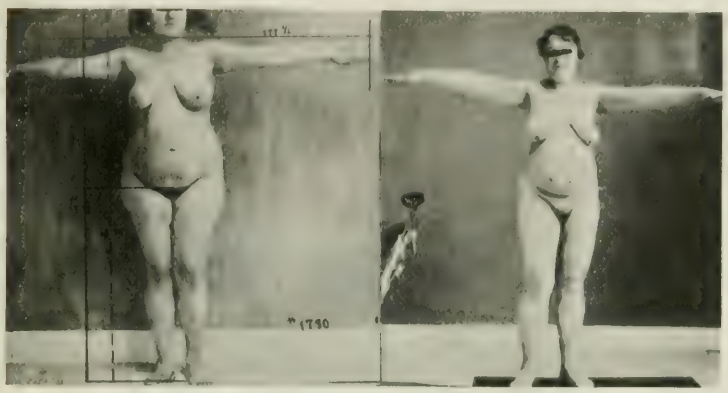

Fig. 17.—Comparison of hypopituitary (left) and hypothyroid (right) adults of the same age. Note the tendency to localization of the adiposity in the girdle region in the pituitary, and the absence of the same in the hypothyroid. In the hypothyroid there is a smooth, even distribution of the panniculus, extending to the dorsa of the hands and feet and cervical region.

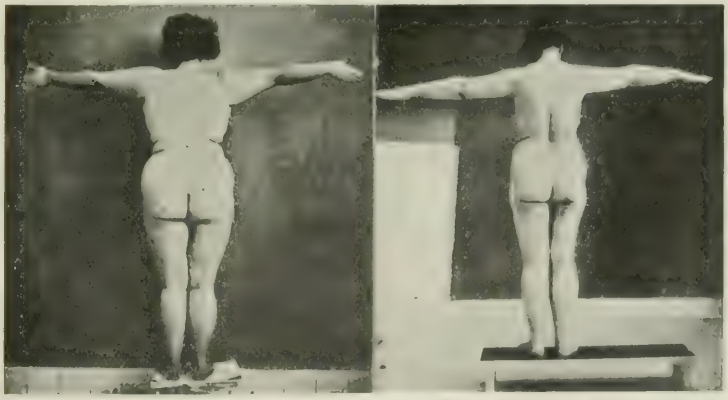

Fig. 18.—Posterior view of Fig. 5. Hypopituitarism (left); hypothyroidism (right). Note particularly the presence of shoulder or deltoid adiposity in the hypopituitary.

fat folding about the lower part of the thorax, particularly in the lateral regions. In those pituitary cases in which there is an

anterior lobe insufficiency, with infantile genitalia, there usually is some slight adiposity in the mammary region, although this is never as marked as it is in the true primary gonad insufficiency. Contrasting with the thyroid cases, the distal extremities (the forearm, hand, leg, and foot) are usually very free from panniculus infiltration. This is also true of the cervical region, which in the pituitary patients is usually free from padding enough to exhibit the bony markings, jugular vein, etc. There is comparatively little mons veneris padding except in those cases in which there

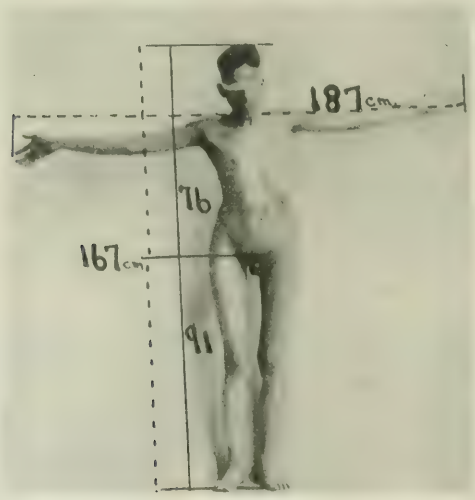

Fig. 19.—Hypogonadism, aged thirty. Same as Figs. 13 and 14. Note the gonad facies, with narrow mandible.

is a secondary hypogonadism due to anterior lobe (pituitary) insufficiency.

In the (*c*) *gonad insufficiency* the most contrasting and striking configuration is the complete absence of adiposity, with the exception of that around the trochanteric region, until the late age of thirty-four or thirty-five. In the early castrates, both men and women, there is a tendency to overgrowth of the long bones and very marked disproportion of the upper (short) in comparison with the lower (long) measurement, with complete

absence of subdermal infiltration, with the exception of the trochanter padding and fulness of the upper thigh. This trochanter adiposity seems to be more decidedly marked and more frequently present in the female than in the male, although the early castrates and eunuchs in the male do show it very characteristically before the age of thirty-four or thirty-five, when the classical gonad adiposity occurs. True gonad obesity consists of disproportionate mammary enlargement as compared with the

Fig. 20.—Female hypogonad, aged twenty-five (complete absence of menses). Note the absence of adiposity, including that of the mammæ at this age, with only slight fulness of the entire thigh. The eunuchoid disproportion of the face and hands and other markings are classic.

adiposity in other portions of the body, but, in addition to this, there is an apron of mons veneris shelving and decided localized trochanter padding, with a diffuse, even fulness of the upper thighs, extending to the knees. The neck, supraclavicular regions, shoulder girdle, and distal extremities are entirely free from fat pads. The disproportionate overgrowth of the long bones is dependent upon the insufficiency of the gonads before the preadult age, or during the epoch at which the ossifying centers are yet actively operating. Should gonad deficiency due

to any cause occur after the age of twenty-five the osseous disproportion could not occur, owing to the fact that the ossifying centers would be inactive at the time of the withdrawal of this inhibitory hormone. A series of illustrations is displayed (Figs. 13, 14, 19, 20) of positive cases from the age of eighteen to forty-three, showing the absence of adiposity up to the age of thirty-four, and its presence after that age. Early female types are also displayed (Figs. 20, 25, 26).

Fig. 21.—Hypogonadism, aged thirty-six. Note the classical gonad adiposity (contrasting with patients of an early age, as Figs. 13, 14, and 19), which occurred at about the age of thirty-four. Previous to this age the patient describes himself as having had a body resembling Fig. 19. Note the classical mammary and trochanter adiposity, with some diffuse panniculus infiltration of the chest and abdomen.

(*d*) *Pluriglandular obesity* consists of a blending or fusing of a number of these typical adiposities in a single individual. It is as if one classical obesity due to a single glandular deficiency were engrafted upon that specific for an entirely different ductless gland. The interpretation of such an apparently complex syndrome becomes fairly easy when the elementary clinical facts concerning the course and signs of each uniglandular adip-

osity are appreciated. In fact, their diagnosis then merely depends upon first carefully separating from the history (age incidence) and physical signs (localization and distribution, etc.) those facts relative to a single glandular disorder, and, second, merging them into one clinical complex. This has been our argument for intensively studying a positive uniglandular disorder and attempting to describe it as simply and with as much minutia as possible, without adding confusion to an already complex and rather vague subject by introducing the interre-

Fig. 22.—Hypogonadism of late adult age. Note the classical adiposity, including that of the mammæ, with overgrowth of the long bones, producing typical enuchoid disproportion. (Courtesy of Drs. H. Enos Tuley and H. H. Turner, Louisville, Kentucky.)

lationship of the endocrine organs and their conceded reciprocal dependence upon the sympathetic nervous system. When once the gross elementary picture produced by the disorder of each of the important ductless glands becomes well known, the analysis of pluriglandular adiposity will consist simply of separating the primary clinical evidence related to each specific internal secretion from the mingled history and markings of these various superimposed obesities. With regard to the adiposity resulting from pluriglandular disorders the age incidence and the localiza-

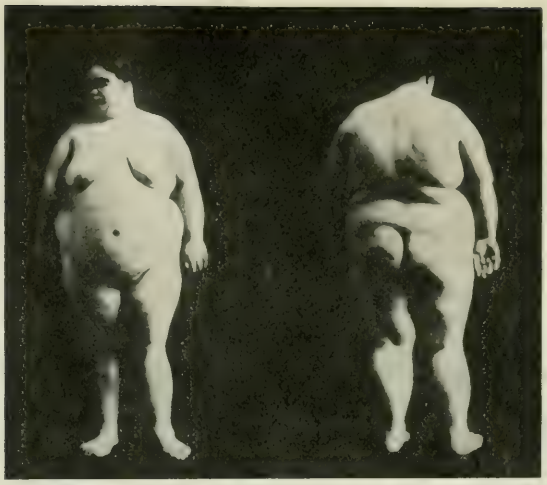

Fig. 23.—Obesity associated with pluriglandular insufficiency (aged forty-three). Adolescent thyroid deficiency, to which was added pituitary deficiency at sixteen, and gonad insufficiency at forty.

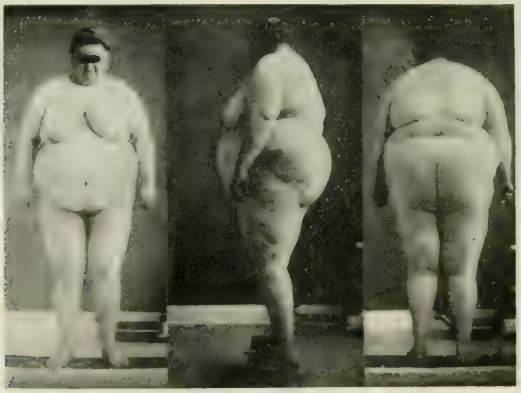

Fig. 24.—Pluriglandular obesity, illustrating a combination of thyroid and pituitary adiposity. The onset of this obesity occurred at the age of thirty-five, with rapid progression following the menopause until the present age (forty-seven).

tion and distribution of uniglandular defects (previously described) are probably the most valuable diagnostic, as well as prognostic, information obtainable. Figures 23, 24, illustrating

a combined deficiency of the pituitary, thyroid, and gonads is a classical example.

Treatment.—The treatment necessarily depends upon *accurate, early diagnosis* of the individual gland involved, or the combination of glandular disorders producing the abnormality in weight. The most important indication in the treatment is its *early institution* at a time when only one gland has been affected, and at which time there is a probability of yet stimulating a physiologic activity of its internal secretion. It is for this reason that so much stress has been placed upon the recognition of these

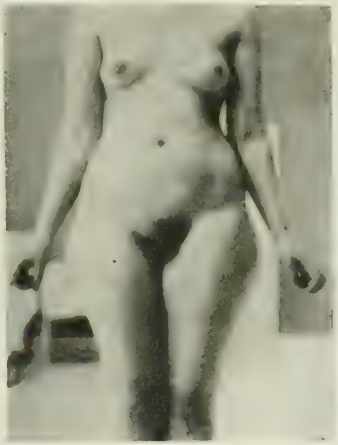

Fig. 25.—Eunuchoidism, demonstrating typical trochanter adiposity.

different adiposities soon after they first establish themselves. A cretin treated during the first six or eight months of its insufficiency unquestionably will react much better than the same individual treated six or eight years after the thyroid gland has been inactive and other glands have been secondarily involved. A pituitary insufficiency treated six or eight months after its onset will have a different therapeutic response than the same deficiency treated eight or ten years after the pituitary gland has become more or less functionless. A hypogonad treated during the adolescent age, when the generative organs are naturally physiologically active, should give a much better

prognosis than the same individual treated at the age of twenty-five or thirty, after the generative organs have been physiologically inactive for ten or fifteen years. In fact, the *late treatment* of these cases *so frequently undertaken* can be compared to the treatment of third stage tuberculosis or inoperable malignancy. This is due solely to the lack of early diagnosis and the proper sense of therapeutic indications. In a general way our limited experience has taught us that, in a certain percentage of cases correctly diagnosed at the onset of their disorder, treatment has

Fig. 26.—Early castrate, aged twenty-eight (castrated at eighteen), demonstrating trochanter adiposity. Note the absence of other adiposity after ten years of castration.

failed for the following reasons: (1) Much of the ductless gland preparation given by mouth probably has been digested in the stomach. (2) Substitution treatment has not been given in sufficient dosage. (3) Treatment by hypodermic injection has not been intensified sufficiently by short intervals between doses. (4) An insufficient amount of the available active principle of these glands has been given subcutaneously or intravenously. In order to avoid digestion in the stomach, ordinary preparations of these various desiccated glandular substances should

be placed in salol-coated or creatinin-coated capsules. This probably to some extent will prevent digestion and allow a more definite therapeutic effect. With the exception of thyroid preparation treatment by mouth alone has been found very unsatisfactory, and resort must be made to the hypodermic use of the active principles of these glands, some of which are available.

The treatment of hypothyroidism is so well known that only a few of the personal aids will be noted. As stated above, in the ordinary case desiccated thyroid substance given by mouth has been effective where therapeutic results can be obtained. In those cases in which the desiccated substance cannot be given by mouth, in somnolent, comatose, or other cases in which treatment per orum is not effective, thyroxin should be used. While it is true that the dosage and interval of giving thyroxin can be more definitely measured by the metabolic rate, the inaccessibility of frequent metabolic readings to most physicians will exclude the use of this specific substance. To an infant less than six months old $\frac{1}{50}$ grain of desiccated thyroid substance once a day is given, and gradually increased by $\frac{1}{50}$ grain until the toxic effect, or until the relief of signs and symptoms is produced. In these infants the toxic effect is measured by the rectal temperature and the weight. An increased rectal temperature or an unusual loss of weight is taken as an indication that too large a dose of thyroid is being administered. The medication should be withdrawn, temporarily at least, to determine whether such signs are due to thyroid intoxication or to any other cause. In the uncontrollable, mentally defective cretin it is very difficult to measure the dosage accurately, for in these patients metabolic readings are almost impossible, and the ordinary clinical signs, such as pulse-rate, temperature, etc., are unreliable. For this reason the rectal temperature and rapid decrease in weight are also considered the best measure of the dosage. In the adult the pulse-rate has been a very simple guide to the first signs of thyroid intoxication. In adult hypothyroidism the pulse-rate ordinarily is slow and the temperature subnormal. A pulse-rate above 100 is considered one of the first indications of thyroid intoxication, and the medication

should be stopped entirely for a few days, the thyroid activity checked by the basal metabolic rate, and the dosage then begun just below that producing such an increase in pulse-rate or in basal metabolism. It is well to know that the therapeutic effect of thyroid is not noted for five to seven days. A help to the treatment is obtained by giving one single large dose a day, instead of breaking the same dose up into fractional ones given three or four times a day, as this relieves somewhat the discipline in those cases in which medication must be carried out for an unlimited duration.

In the pituitary cases our indications for dosage and frequency of treatment have not changed from those previously published,[1] at which time we attempted to define three types of physiologic reaction, the "intestinal," the "vascular," and the "general." The "intestinal" reaction to pituitrin evidences itself by a cramping, colicky sensation in the abdomen, succeeded within a few minutes by bowel evacuation. This "intestinal" reaction usually begins within five minutes and rarely occurs later than fifteen minutes after the injection of a sufficient amount of pituitrin. It has been the writer's custom to begin in adults with a dose of pituitrin 5 minims (0.3) and gradually increase it 1 minim (0.06) each day until the "intestinal" reaction is produced. This dosage is then considered the tolerant physiologic dose sufficient to overcome the deficiency of the gland. In infants and children 1 minim (0.06), or, if below one year of age, a fraction of a minim, is used as the initial dose. When this extract is given by mouth the adult is started with 15 to 20 minims (1–1.3) a day, and the dosage increased 2 to 3 minims (0.12–0.18) each day until the "intestinal" reaction above described is obtained. This dosage is then continued, and careful observations made upon the weight, circumference measurements, etc., for a number of weeks, to determine its effect upon the obesity and other symptomatology. If, after two or three months of intensive treatment, with a carefully measured tolerant dose, there has been no decided effect upon the signs of adiposity

[1] Pituitary Polyuria (Diabetes Insipidus), Engelbach and Tierney, Int. Clinics, iv, S. 30, 1920.

or the chief complaints, the case is considered one not reacting to treatment. Besides the hypodermic administration of pituitrin extract the entire gland substance is given by mouth, pituitary substance, in salol- or creatinin-coated capsules, in dosage of 10 to 30 grains (0.6–2) after meals. The writers have never observed "intestinal," "vascular," or "general" reactions from the oral administration of this substance. It is understood that substitution of pituitrin or pituitary substance, as described, is indicated only in those cases in which there is definite hyposecretion or insufficiency of the infundibulum or the posterior lobe of the hypophysis.

Gonad insufficiency in the male has never been successfully relieved by treatment under our observation. We must qualify this by saying that prolonged observation has been made on the effects of various orchic substances given only by mouth. Recently we have used various orchic substances hypodermically, but regarding these we have had neither the material nor the length of time for drawing conclusions. The same statement applies to pineal and pituitary treatment in these cases. While we have had a considerable number of cases under observation, thus far the time has been so limited as not to warrant conclusions concerning their effects. In the female gonad insufficiency, notwithstanding the many contrary reports of the literature, we feel confident many good results have been accomplished by simple substitution treatment. These effects have been produced in early and late castrates, menopause cases, and the partial insufficiencies occurring in eunuchoid or postoperative females. Detailed descriptions of a large series of these cases will soon be ready for publication. The treatment should consist of much larger doses of ovarian substances than ordinarily given. After prolonged trial of various parts of the ovaries, such as the corpus luteum and preparations of the stroma of the ovary, we have finally concluded that the substance of the entire ovary is more efficacious in the average case than any preparation made from its various parts. Consequently, for the past few years we have been giving ovarian substance in large doses, 10 to 20 grains (0.6–1.2), four or five times a day. Besides this, ovarian

substance should be given hypodermically, in doses from 1 to 5 or 6 c.c. daily. In exceptional cases a large dose given intravenously has a more rapid, but not so prolonged an effect as that given subcutaneously. The size of the dose and its frequency must be determined almost entirely by the reaction of the patient. In some cases a dose given once or twice a week has been fairly effective. In others 4 to 6 c.c. must be given daily in order to produce any appreciable effect.

The treatment of the adiposity associated with pluriglandular insufficiency consists simply of a combination of the uniglandular therapy described above, which is indicated by the number of glands involved in the complex. We do not believe it advisable, however, to begin the treatment with a number of different glandular preparations given at the same time. Even in these pluriglandular syndromes we have always advised the use of the preparation of the active principle of a single gland in order to determine the specific effects, if any, upon the symptomatology. After giving this preparation in tolerant dosage for a sufficient length of time to be able to observe any action it might have upon the symptoms or physical signs, the preparations from other ductless glands thought to be involved in the production of symptoms are given successively, either singly or in combination with that of the initial gland, the effects of which have already been estimated. It is best to begin the treatment with that internal secretion the insufficiency of which initiated the complex; or, in serious cases, with the preparation of that gland whose disorder is producing the most distressing symptomatology. After the maximum effect of one glandular substance has been obtained it is a good plan in many instances to withdraw this preparation entirely and give a single substance from another gland, noting the therapeutic reaction in the reduction of obesity, measurements, and symptoms. After one is convinced of the potency of the preparations and the good effects obtained from a number of glandular substances, these can then be combined and given to the patient at the same time. This is done as a check upon the diagnosis, as well as to determine the actual indications for a single glandular preparation. We are convinced

that the early, prolonged use of uniglandular treatment, as described above, even in these pluriglandular syndromes, when careful observations of their measurable effects are made, will be of the greatest aid not only in estimating the indications by the value of the treatment of the endocrine disorders but also in helping to fix the diagnosis in many of these complex clinical entities.

In addition to the above endocrine treatment, ordinary dietetic schemes, consisting of a very low carbohydrate and fat-free diet, besides the accepted hygienic and hydrotherapeutic measures, should be considered.

CLINIC OF DR. JOHN L. TIERNEY*

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PUBERTAS PRÆCOX

Precocious Puberty Considered Etiologically: (*a*) Gonad. (*b*) Adrenal Cortex. (*c*) Pineal. (*d*) Differential Diagnostic Table. (*e*) Presentation of Typical Cases. (*f*) Conclusions.

The condition *pubertas præcox*, precocious puberty, or, when associated with precocious somatic development, the so-called syndrome *macrogenitosomia præcox*, has received the attention of many observers, and etiologically the state has been attributed to disturbed function of various endocrines, notably the gonads, adrenal cortex, and pineal gland.

Leiner,[1] in a recent review, quotes Anthony White[2] to the effect that the condition was recognized among the ancients. Craterus,[3] the brother of King Antigonus, describing the condition, wrote, "The subject was an infant, a young man, a mature man, an old man, was married and begat children, and all in the space of seven years." Pliny[4] the elder mentioned a number of such cases in his chronicles. In 1747 Mead[5] presented before the Royal Society of London such a boy, remarkable for his bulk and height, and presenting the external marks of puberty at the age of twelve months. White himself, in 1811, described in detail the case of Philip Howarth, who, at the age of two years, weighed 47 pounds and was 3 feet, 2 inches in height. At three years the height was 3 feet, 4½ inches and the weight 51¼ pounds. There was likewise precocious sexual and mental development. Apert[6] states that Otto (1816) found hypertrophy of the genitalia associated with adrenal hypertrophy.

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Plumb[7] and Stone[8] have reported cases showing the possibility of hereditary transmission. Although many cases in the literature are inadequately studied, there is definite unanimity in referring this condition to hypersecretion of the gonads, adrenal cortex, or pineal, although it is admitted that probably the pituitary and the thyroid are concerned.

Gonad.—Leiner reports Rogers[9] as having collected 101 cases of pubertas præcox, 81 females and 20 males. Of the 81 female cases, 73 appeared to be mostly due to hyperovarianism. Krabbe,[10] Wells,[11] Lenz,[12] and Bruno Wolff[13] have reported similar cases. Lucas[14] reports a case of tumor of the ovary associated with this syndrome, which disappeared following operation. Gaudier[15] reports a tumor of the ovary resembling a suprarenal cortical neoplasm, giving rise to sexual precocity. Roger Williams[16] collected 11 additional cases in female children due to ovarian tumor. In none of these cases was there a tendency to mental precocity. Sacchi[17] reports a case in association with enlargement of the left testicle, in whom puberty occurred at five years of age. At the age of nine his height was 5 feet, 6 inches and his weight 97 pounds. He had an unusual physical and muscular development, a black beard 5 cm. in length, and full sexual development. The tumor was excised and diagnosed alveolar carcinoma. After removal the beard disappeared and regressive changes in the genitalia occured. Breschet,[18] Woods,[19] and Lopez[20] have reported similar cases. Strauch[21] reports a case possibly to be included in this classification. Numerous observers are agreed that in this type of cases there is no mental precocity, but rather a tendency to decreased function, and even to imbecility. In hypergonadism in the female we find early menstruation, premature ossification and epiphyseal closure, and short stature; in the male, similar bony changes, accentuated male characteristics, primary and secondary, spermatogenesis, and unusual physical strength.

Adrenal Cortex.—Glynn[22] quotes 12 cases of sex abnormality in children associated with adrenal hypernephroma, verified postmortem, and adds 5 additional cases, concluding from this series that hypernephroma of the adrenal in children is much

more common in females, and also tends to increase male primary and secondary sexual characters at the expense of the female (having noted the occurrence of beards in several of the female children, the usual absence of menstruation, and hypertrophy of the clitoris; also the greater muscular development of the male children).

It is to be noted that adrenal hyperplasia or neoplasia is rather constantly associated with diminution of the female and increase of the male primary and secondary sex characters. The converse does not occur; for in males, on the contrary, the masculinity usually increases. Bell[23] believes that many of the cases of sexual precocity in the female, attributed to hyperplasia or tumor of the suprarenal cortex, are really not cases of true feminine precocity, but rather of masculinity, and that the appearance of hair on the pubes and other signs of puberty may have no relation to feminine precocity, but rather to the change to masculinity which may be produced in a true female or in a female partial hermaphrodite. Pitman,[24] Orth,[25] and Dobbertin[26] report similar cases in the female. In Glynn's series of 17 cases but one occurred in the male, reported by Linser,[27] death occurring at the age of five, the first symptoms appearing at one and one-quarter years (pubic hair present, general development and weight of a boy of fifteen, precocious sexual development, sexual activity; nature of tumor, hypernephroma).

Pineal.—McCord,[28] writing in 1917, states that up until that time only 70 cases of tumor of the pineal had been reported, and of these, only 22 occurred before the age of puberty. In 1907 Marburg[29] had collected 40 such types, and sought to establish a clinical entity for pineal dysfunction. In 1909 Frankl-Hochwart[30] suggested the possibility of a pathognomonic syndrome. Marburg,[29] in a later paper, outlined the symptomatology under three headings: (1) general (these included all the usual signs of intracranial pressure, due to a secondary hydrocephalus); (2) neighborhood (these, for the most part, are dependent on pressure upon the quadrigeminal bodies, giving various oculomotor paralyses and pupillary dis-

turbances, and also ataxic manifestations when the cerebellum is encroached upon); and(3) constitutional (consisting of general body overgrowth, early sexual maturity, genitalia frequently of adult proportions, proportionate development of secondary sexual characteristics, including pubic and axillary hair and early change of the voice, and precocious mental development). Frankl-Hochwart, in a summary, states that, when one finds in a very young individual, along with the general signs of tumor, as well as signs of lesion of the corpora quadrigemina, abnormal body growth, unusual growth of hair, adiposity, somnolence, premature genital and sexual development, and, finally, intellectual maturity, one must think of pineal tumor. Of the 22 cases occurring prior to puberty, all were males with the exception of 2.

Neumann[31] up to 1901 had collected 22 cases from the literature, 19 males, and 3 females, the majority being in children. Nearly half of them were sarcoma, with carcinoma and teratoma being next most common. Comparatively few of these occurring prior to puberty have been associated with precocious sexual change. Bailey and Jellife[32] collected 60 cases of pineal tumor, including their own, 17 of whom showed involvement up to the age of sixteen. Of these, 14 were male and 3 female.

It is evident from a perusal of the literature that improper consideration has been given to the possibility of other glandular involvement. In fact, in some of the cases the demonstration of pineal tumor led to the assumption that all changes were due to this abnormality. *Glynn, up until 1912*, was able to find *only 5 cases* of pineal tumor proved by autopsy, in children, *associated with sexual precocity*, all occurring in boys. These cases are those reported by Ogle,[33] Oestreich and Slawyk,[34] Gutzeit,[35] Frankl-Hochwart, and Raymond and Claude,[36] and all are included in Bailey and Jellife's compilation. These cases all showed precocious sexual development, with the exception of that reported by Raymond and Claude, which showed abnormally small testes and penis.

Kidd[37] quotes Pellizzi[38] and Machell[39] as having reported

3 cases. Morse[40] reports a case of macrogenitosomia præcox in a boy of twenty-three months, but is in doubt as to whether the condition is due to an adrenal tumor or to an involvement of the pineal. The absence of intracranial signs and the dull mentality, he feels, point to adrenal rather than to pineal involvement.

Horrax[41] reports 3 cases, 1 in a girl aged eleven, with precocious body and sexual development, menses occurring at eleven, with considerable question as to whether the pineal is the organ primarily at fault. The second case is a boy aged seven and a half years, who complained of precocious adolescence and epilepsy. His general appearance was that of a boy of fifteen or sixteen, weighing 77½ pounds, 4 feet, 9 inches in height (down on the upper lip, thick pubic hair of masculine type, marked overdevelopment of the genitalia—penis flaccid, 9 cm. in length). In this case, too, there was no positive evidence of pineal involvement. The third case is one of precocious adolescence, with intracranial symptomatology, suspect pineal tumor, aged twelve, 97 pounds in weight, 5 feet, 3 inches in height (external genitalia overdeveloped, long bones noticeably enlarged, normal sella turcica, precocious mentality, without adiposity). In this case necropsy disclosed a struma of the pineal gland. It will be noted that no adiposity was present, a point upon which Marburg lays considerable stress.

Horrax quotes Kidd as follows: "Even absence of any recognizable histologic changes in the pituitary or other glands in such cases does not exclude the possibility of associated dyspituitarism due to subtle metabolic or chemical changes, of which, at present, we have no knowledge. Then, again, adiposity occurs in so many other conditions, and its modes of production are still so obscure, that we must conclude, I think, that there is uncertainty whether hyperpinealism in man ever causes adiposity *per se*." In this connection it will be noted that our 4 cases of pubertas præcox have shown no striking adiposity.

Cushing[42] reports a case aged eight, overgrown, 5 feet, 6 inches in height, adipose, weighing 95 pounds (blind, large

headed, with hypertrophied genitalia, left-sided ptosis, with divergent squint, hypertrichosis). Section of the testes showed a preadolescent type of tubule and a great excess of interstitial cells. Radiogram of the sella turcica was negative, as was pineal exploration.

In regard to the experimental work done upon the pineal gland in its relationship to somatic and sexual development, there is considerable disagreement. According to Dandy,[43] experimental extirpation of the gland is surgically possible, and the gland is not essential to the maintenance of life. Early symptoms following pinealectomy are attributable to severe brain injury. No changes attend removal of the gland in adult animals. In young animals, Sarteschi,[44] Foà,[45] and Horrax state that the removal of the gland leads to precocity of development. Exner and Boese[46] and Dandy report no changes after pinealectomy.

Dana and Berkeley,[47] in conjunction with Goddard and Cornell, conclude that the ingestion of powder made from the pineal body hastens the growth of young animals, especially guinea-pigs, kittens, and young rabbits. McCord,[28] feeding the powdered extract of the pineal gland of young adult cattle, dried and mixed with lactose, found an appreciable overgrowth in body weight. Later, substituting hypodermic injections, he found similar results. In unicellular organisms, for instance, paramecia, pineal extracts increase the rate of reproduction to more than double that of controls. In larval forms of frogs, both growth and differential were hastened as a result of pineal feeding; and he draws the conclusion that the pineal gland is an organ of internal secretion, the functions of which, however, are of minor significance in the general activity of the endocrine system.

Horrax found that intravenous injections of extracts of the pineal body of young animals caused constant, but relatively slight, fall in pressure; and J. B. Boehm,[48] studying the prolonged effects of the oral administration, found conflicting results. In some cases the fed animal showed greater development of the genital organs than the control; while in other

cases the control outstripped the animal to which the pineal was administered. Dana and Berkeley also found that feeding backward children, without organic stigmata, for periods of three to six months caused an advance in mental age considerably in excess of any previous progress for a like period. It thus may be seen, from experimental work, that there is considerable doubt as to whether hypopinealism or hyperpinealism is a factor in the production of the syndrome under discussion, or whether the pineal gland has any influence one way or the other. To reach a satisfactory conclusion as to such etiology there certainly must be a more definite study concerning the differential points, if there be differential points.

There seem to be a number of well-authenticated cases of hypergonadism in the production of this syndrome in both the male and the female, the outstanding feature being early *epiphyseal closure* and *ossification*, retarded mentality, and early menstruation in the female, with and without actual tumor of the ovary or testicle. There are, especially in the female, many cases having adrenal pathology to account for the condition, the outstanding features, in addition to the precocious somatic and sexual development, being the absence of menstruation, the hypertrichosis and tendency to masculinity, the dull mentality, and no abnormality of bony development. In regard to the pineal there are but few well-authenticated cases, and in these the study has not been sufficiently general to definitely conclude that the pineal constitutes the sole etiologic factor. If these cases be accepted, the outstanding features are, in addition to the precocious sexual and somatic development, a *precocious mentality* and an *intracranial* symptomatology, with relative infrequency in the female.

The following 4 cases are submitted as an interesting clinical study, especially from the differential diagnostic standpoint.

Case I.—Master J. C., aged four years and four months. Referred by Dr. B. D. Ravdin, Evansville, Indiana.

Chief Complaints.—(1) Somatic and genital overdevelopment. (2) Somnolence. (3) Enuresis. (4) Polydipsia, polyphagia, and polyuria. (5) Mental backwardness.

PUBERTAS PRÆCOX

Table of Differential Signs

	Occurrence.	Sex characters.	Osseous changes.	Trichosis.	Menses.	Mentality.	Intracranial signs.
Gonad.	More frequent in female.	Precocious, but true to sex type.	Premature ossification and epiphyseal closure. Stature short and stocky.	Hypertrichosis, but true to type.	Early.	Normal or subnormal.	Absent.
Adrenal.	More frequent in female.	In female, tendency to male type. In male, accentuation of male characters.	No marked change.	Hypertrichosis, but in female tendency to male type. In male, true to sex type.	Late or absent.	Subnormal.	Absent.
Pineal.	More frequent in male.	Precocious, but true to sex type.	Tendency to overgrowth. Ossification and epiphyseal closure not premature.	Hypertrichosis, but true to type.		Precocious.	Usually present.

Course.—The patient was extremely large at birth, weighing 12½ pounds. General development was very rapid At the age of one year he weighed 21 pounds; at two years, 42 pounds; and at three years, 52 pounds. First teeth erupted at six months, and the patient walked at fifteen months and talked at twelve. At two years there was noted definite overgrowth of the genitalia. This unusually rapid development has progressed, until at the present time, at the age of four years and four months, the patient weighs 81 pounds. He is larger than a brother aged twelve, wears the same size of clothing, shoes one size larger.

A B

Fig. 27.—A. Case I, aged four and a half, contrasted with normal ten-year-old boy. B. Contrast of Case I with normal boy four and a half years old.

Mental development has been fair. The patient is abnormally strong, extremely active, restless and energetic, but easily controlled. Appetite is very good. There is tendency to enuresis and to polyuria and polydipsia.

Past History. No illnesses except an acute mastoiditis, with operation. *Personal:* Appetite good, bowels regular, patient sleeps well. *Family:* Father of short, stocky build; has large hands and feet, with tendency to acromegalic type.

Mother also short and stocky, with tendency to obesity. Two sisters and two brothers well, without apparent endocrine abnormality.

Physical Examination.—Aged four years, four months. Weight, 81 pounds. Symphysis to soles of feet, 23½ inches (59½ cm.); symphysis to vertex, 26½ inches (67 cm.); span, 53 inches (134½ cm.). General development remarkably disproportionate to age, stature that of boy of twelve. Increased growth of hair about legs and forearms, none about chest. Extensive pubic hair, feminine type of distribution, axillary hair abundant. Genitalia, both penis and testes show development of normal adult; left testicle irregular in size, very hard

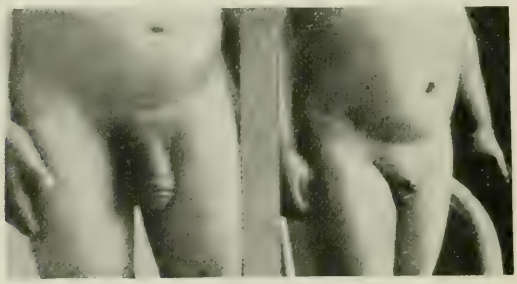


Fig. 28.—Contrast of genitalia of Case I with genitalia of normal boy four and a half years old.

in consistency, about size of English walnut, epididymis distinctly palpable; right testicle about half this size, firm, hard in consistency, and slightly nodular. Marked growth of hair about face and upper lip. Brownish pigmentation about forehead limited to hairline. Color about body lardaceous. *Regional:* Head well formed, round type of face. Hair dry. Eyebrows thick, meeting in midline, palpebral slits narrow, with slight slant, suggesting Mongolian type. Nose shows moderate high saddling. Definite growth of hair on upper lip, lips thick. No permanent teeth manifest, definite separation of upper incisors, of lateral incisors from canines, and of lower central incisors; canines markedly prominent, out of proportion to other teeth. Thyroid not enlarged. Chest, including lungs and heart, nega-

tive; peripheral vascular system negative. Blood-pressure, 180/115, on first observation; two days later, 140/80. Abdomen negative. Genitalia: Penis, in unerect state, $3\frac{3}{4}$ inches ($9\frac{1}{2}$ cm.) in length; left testicle, 2 inches (5 cm.) in length; right testicle, $1\frac{1}{4}$ inches (3 cm.). Left testicle particularly hard in consistency, nodular. Prostate palpable. Neurologic examination negative.

Urine, single and twenty-four-hour specimens, negative except for few pus and epithelial cells. *Blood:* hemoglobin, 67 per cent.; leukocytes, 9800; erythrocytes, 4,530,000; Wassermann negative. Differential count: polymorphonuclears, 50 per cent.; large lymphocytes, 20 per cent.; small lymphocytes, 29 per cent.; transitionals, 1 per cent. *Non-protein nitrogen,* 31 mgm. per 100 c.c. *Sugar tolerance test:* Blood-sugar after fifteen-hour fast, 0.070 per cent.; one hour later and following ingestion of 1.59 gm. dextrose per kilogram of body weight, 0.150 per cent. *Basal metabolic rate,* —8 per cent.

Fluoroscopic examination of head and chest shows no abnormalities, including thymus. *Radiograms* show *kidneys* normal in size and position. *Radiogram of skull,* transverse view, shows sella turcica somewhat large, no evidence of excavation or erosion; no abnormal shadows in pineal area. *x-Ray of hand* shows marked advance in development of metacarpal bones and all carpal centers present, from hamate and capitate (appearing in third year) to pisiform (which normally does not appear until twelfth year), although epiphyseal junctures not completely closed.

Electrocardiographic examination, suggestion of right ventricular preponderance.

Ocular examination by Dr. John Green, Jr., shows hyperopic astigmatism, no impairment of ocular muscles or contraction of visual fields. Ophthalmoscopic examination shows well-marked adult type of eye-grounds, with marked pigment on nasal and temporal margins. Fundus presents adult type of stippling, with none of shot silk reflexes invariably present in eyes of so young a person.

Radiation to the pineal and adrenal glands, and pituitary substance, entire gland (Parke, Davis & Company), 5 grains,

and pineal substance (Parke, Davis & Company) ¼ grain, by mouth, three times a day, after meals, up to the present have wrought no perceptible change in the patient's general condition.

Discussion.—This case, a boy aged four and a half years, weighing 81 pounds, and 4 feet, 2 inches in height, with ab-

Fig. 29.—Skiagraph of hand and wrist, Case I (aged four and a half). Note heavy, dense character of bone, and presence of all carpal centers, from hamate and capitate (which appear during the first year) to pisiform (which normally does not appear until twelfth year). Practically complete epiphyseal closure of metacarpals (which ordinarily does not occur until twentieth year). Epiphyseal lines of radius and ulna are not closed, but are faintly indicated.

normal strength, retarded mentality, premature ossification, and nodular character of testicle, suggests hypergonadism as the outstanding etiologic factor. The hypertrichosis and the arterial hypertension, with absence of other demonstrable

causation, suggest involvement of the adrenal cortex, although there is no evidence of adrenal tumor. The absence of intracranial symptomatology and the retarded mentality speak against the pineal gland as an etiologic consideration.

Fig. 30.—Hand of normal boy four and a half years old, showing centers normally present for age. Lower extremity of ulna (which normally appears during fourth year) not indicated. Contrast with heavy center in Fig. 29.

Case II.—Master R. B., aged six, referred by Dr. E. S. Kilpatrick, of Elk City, Oklahoma.

Chief Complaints.—(1) Precocious physical and sexual development. (2) Epileptiform seizures. (3) Increased nervousness. *Duration*, from birth. Birth was premature, five or six weeks before the full term. The weight at birth was 9½ pounds. The baby was artificially fed, and for the first three months

lost weight and was poorly nourished. He then began to grow very rapidly, with consistent and proportionate overgrowth of the entire body. The genitalia, unusually large at birth, continued to grow, and now have the development of a sixteen- or seventeen-year-old boy. The child is extremely temperamental, difficult to manage, and requires constant attention to prevent damage. He is moody, with tendency to brainstorms and to be destructive, breaking furniture, etc. He plays with other children, but is inclined to be a tease, and is usually not in harmony. The voice became hoarse and of bass quality at the age of three. The secondary sex characters, with abnormal hair growth, appeared at the same time, with an augmented growth of the genitalia. Erections have occurred, and the father believes that the boy has indulged to some extent in masturbation. Since birth a peculiar nervousness and tremulousness has been noted. Later definite attacks of petit mal occurred, and occasionally grand mal, with definite contractions, preceded by an aura and complete unconsciousness, but no history of frothing at the mouth or tongue biting. Unconsciousness has lasted as long as three or four hours. Attacks have occurred with varying frequency, sometimes as often as two a day, at other times at intervals of three weeks to three months. Mentality is below par.

Past History.—No childhood diseases. Influenza in 1917, complicated by pneumonia. Following this, epileptiform attacks ceased for a period of two and a half months, and severe attacks did not occur for a year. Adenoids removed and circumcision done at the age of three. *Personal history* unimportant.

Family History.—First two children in the family were stillborn. Third child, a girl of eight years, shows no abnormalities. Patient is the fourth child. Father obese, weighing 246 pounds, 5 feet, 8 inches in height. Mother of no particular endocrine type. No other family history of importance.

Physical Examination.—Aged six. Markedly overgrown boy, weighing 79 pounds. Height, 4 feet, 8 inches. Symphysis to soles of feet, 27 inches (68¼ cm.); symphysis to vertex, 29 inches

(73½ cm.); span, 54½ inches (138¼ cm.). Persistence of infantile measurements. Patient extremely nervous and restless during course of observation. Mentality poor, some tendency to speech defect. Secondary sex characters very well developed. Genitalia show marked precocity of development. Skin shows no abnormal pigmentation or texture. Hand, palm broad, fingers proportionately long, tapering, lunular markings not visible,

Fig. 31.—Case II, aged six, supported by father, giving some idea of somatic development. Note imbecile expression, increased hair distribution about lower extremities, precocious genitalia, and atypical pubic hair.

slight padding on dorsa of hands. *Regional:* Head large, symmetric. Hair of coarse texture, dry. Faint brownish pigmentation about forehead, limited to hairline. Lanugal growth about cheeks and definite growth on upper lip and chin. Slight mandibular prognathism. Eyebrows very thick, meet in midline. Some fulness of upper lids. Palpebral slits narrow. Pupils unequal, right larger, very slightly irregular in contour, but react promptly to light and accommodation. Eye muscles

intact. Lips thick. Dentition poor, molars and canines barely appearing through gums; both upper and lower central incisors large, serrated, and separated. Tonsils hypertrophied. Thyroid not palpable. Lungs and heart negative. No changes in peripheral vascular system. Blood-pressure, 85/60. Genitalia markedly enlarged: in flaccid condition, penis $4\frac{3}{4}$ inches (12 cm.) in length; testes, epididymi, and vas well developed. Moderately heavy growth of pubic and axillary hair. Well developed prostate. Neurologic examination negative.

Urine negative except for an occasional pus-cell. *Blood:* Leukocytes, 11,000; erythrocytes, 5,690,000; Wassermann negative. *Sugar tolerance test:* Blood-sugar after fifteen-hour fast, 0.080 per cent.; one hour later and following ingestion of 1.59 gm. dextrose per kilogram of body weight, 0.130 per cent.; two hours after dextrose, 0.100 per cent. *Adrenalin (Goetsch) test* shows increase in systolic pressure of 12 points, and in diastolic, of 5; in pulse-rate, 12 per minute. During test, some palpitation, general excitability, flushed face, pallor, and increased restlessness. *Pituitrin test* shows increase in systolic blood-pressure of 15 points, and in diastolic, of 10; pulse, 15 per minute. During test, increased perspiration, flushing, and restlessness.

Fig. 32.—Figure on right shows genitalia of Case II, aged six; figure on left, of male aged thirty, representing the opposite type, hypogonadism, with classical eunuchoid make-up, scant pubic hair, infantile genitalia, high-pitched voice, etc.

Fluoroscopic examination of chest shows no abnormalities. *Radiograph of chest* shows no abnormal shadows in thymic area. *Transverse view of skull* shows shallow sella turcica,

Fig. 33.—Skiagraph of hand and wrist of Case II (aged six). All carpal centers seen, from those that normally appear in first year to those that do not normally appear until twelfth year. Practically complete closure of epiphyseal lines of ulna and radius (which normally does not occur until eighteenth or twentieth year). Likewise epiphyseal closure of metacarpals (which does not occur until twentieth year).

4 mm. in depth; anteroposterior diameter, 10 mm.; anterior and posterior clinoid processes distinctly seen, no evidence of erosion. *Radiograph of hand and wrist* shows all carpal centers fully developed, premature ossification, all epiphyses closed

throughout hand. Practically complete closure of radius and ulna, which normally should not occur until eighteenth or twentieth year.

Ophthalmologic examination by Dr. John Green, Jr., shows normal vision. Extreme muscular power in orbicularis, no

Fig. 34.—Contrast of hand of normal six-year-old boy. Note character of carpal bones, only those centers that normally should be present are seen. Hamate and capitate fairly well developed, others small. Epiphyseal lines clearly indicated. Contrast with heavy, well-formed center, Fig. 33.

diplopia or hemianopsia. Eye-ground shows adult type of fundus, well-marked demarcation of disk, no engorgement. Foveæ normal. Complete absence of shot silk reflexes characteristic of youthful fundi.

Neurologic examination by Dr. Francis M. Barnes, Jr., shows no striking abnormalities. Mental age, roughly deter-

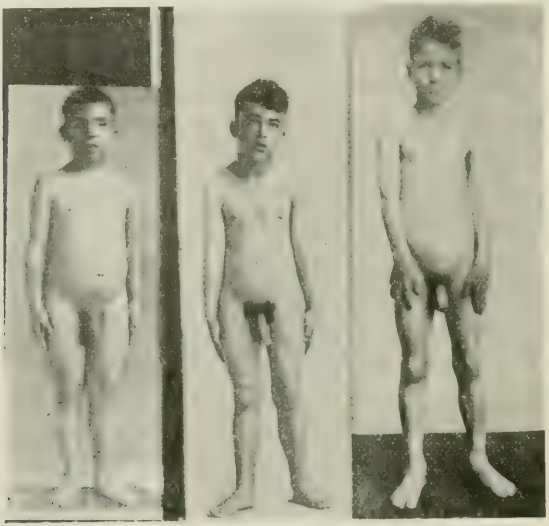
mined, between four and five years. Examination shows speech disturbance, unusually well-developed musculature, and peculiar movements of upper extremities. Psychic examination shows abnormal behavior and conduct, inaccessibility, lack of cooperation, lowered attention and stability, disturbance of facility and sequence of train of thought, impaired critique and judgment, emotional instability, with marked fluctuations, inadequate insight, and a mental development of between four and five years.

The patient was placed upon sodium bromid and luminol, and given *x*-ray radiations as follows: area selected, temporal region and forehead, and beneath the ear, anteriorly and posteriorly, beneath the hairline, so as to avoid the alopecia resulting from *x*-ray exposures to the scalp; 9-inch tube distance, 5-milliampere current, ten-minute time exposure, with 5-millimeter aluminum filter. Treatments were given every five days. Fourteen were given in all, at the conclusion of which a report from the local physician states that the boy seemed much brighter and more active, attacks of petit mal had disappeared, and attacks of grand mal had been reduced about 50 per cent. His temper, however, seemed more violent, and the boy was more difficult to control. A communication received nine months later, and after the patient had been on pineal substance (Parke, Davis & Company) by mouth, states that the general appearance is much brighter and more intelligent. The patient has developed a desire to run and play with other children, and likes to have company; whereas formerly he had been extremely reticent. Petit mal attacks have almost entirely disappeared, and grand mal attacks are very much less in frequency and severity.

Discussion.—In this case the precocious physical and sexual development, the decreased mentality, the premature ossification, and the epiphyseal closure suggest hypergonadism. There is nothing particularly suggestive of adrenal involvement. The epileptiform seizures suggest intracranial pathology, but not pointing particularly to pineal involvement. The decreased mentality rather speaks against this type.

Case III.—Master H. R., aged ten, seen in consultation with Dr. W. McKim Marriott, Children's Hospital, St. Louis.*

Chief Complaints.—(1) Precocious physical and sexual development. (2) Deficient mentality. The patient was a full-term baby, with instrumental delivery. Early development is unknown. He has always seemed mentally deficient. He willingly does what he is told, but instructions must be frequently repeated. Memory is poor. He has been in the



A B C

Fig. 35.—A. Case I (aged four and a half). B. Case II (aged six). C. Case III (aged ten). Note similar characteristics, precocious somatic and genital development.

first grade at school for three years. He works diligently at his studies, but cannot seem to master them. He is not destructive or difficult to control. Precocious sexual development was noted at an early age, no masturbation known. The child is subject to frequent attacks of screaming. Marked fright reaction to familiar objects.

* Reported through the courtesy of Drs. Marriott and Clausen, Children's Hospital, St. Louis.

Examination.—Extremely large for age, with precocious genital development. Peculiar facial expression and definite mental abnormality. Build short and heavy. Head low and wide. Nose broad at base and flat. Hands spade-like, thumbs short and stubby, palms broad, fingers short and thick. Hair coarse and dry. Chest negative. Abdomen negative except for imperfectly healed umbilicus and diastasis recti. Liver palpable just below costal margin. Long, coarse hair about genitalia, marked overdevelopment of penis and scrotum, testes of size and consistency of adult. Neurologic examination negative, except that patellas and Achilles seem hyperactive.

Ophthalmologic examination negative.

Mental examination by Dr. G. B. Smith: Yerkes-Bridges point-scale examination. Total score, 17. Mental age level, four years. Reactions, both as to manner and type of response, feeble-minded, of an inherited type. Impression of feeble-mindedness, mild grade imbecile, congenital, possibly secondary to disordered metabolism.

Urine and *blood* negative. *Sugar tolerance:* 0.8 gm. glucose per pound of body weight. Blood-sugar after fasting, 0.088 per cent.; first hour, 0.146 per cent.; third hour, 0.082 per cent.—with no glycosuria. Second test performed with 1.2 gm. glucose per pound of body weight: Blood-sugar after fasting, 0.086 per cent.; first hour, 0.082 per cent.; second hour, 0.094 per cent.; third hour, 0.084 per cent. (negative glycosuria), showing definitely increased tolerance. *Basal metabolic rate* normal. Lumbar puncture: Spinal fluid clear; under normal pressure, cell count 3 per cu.mm.; globulin negative; Wassermann negative; Lange colloidal gold negative. *Adrenalin (Goetsch) test* shows definitely positive response, increase of systolic pressure from 110 to 200; of diastolic, from 65 to 90; increase in pulse-rate from 72 to 112 (without subjective symptomatology except slight fulness in head). Urine negative for dextrose both before and after adrenalin. Control test: A patient of same age, given same dose of adrenalin (0.5 c.c. of 1 : 1000 solution), showing rise in pulse-rate of 20 per minute, and in blood-pressure of only 15 mm. Hg.

Stereoscopic plates of skull show calvarium generally thickened and coronal suture closed; sella turcica deeply and vertically placed, but small. Sphenoid antrum not developed, and lambdoid suture not made out.

Discussion.—In this case the precocious physical and sexual development, the deficient mentality, and the apparently premature ossification suggest hypergonadism. There is nothing particularly suggestive of adrenal involvement, unless, perhaps, the violent reaction to adrenalin hypodermically may be significant. There is no intracranial symptomatology or precocious mentality to suggest primary pineal involvement.

Case IV.—Miss J. S., aged fifteen.

Chief Complaints.—(1) Precocious sexual development. (2) Retardation of osseous development, particularly of the long bones. Birth was normal, and, according to the mother, dentition, walking, and talking occurred at the normal time. The first tooth appeared at eight months, and the patient walked at twelve months, and talked at about the age of two years. The menses began at the age of six months, with very slight evidence of blood on the napkin, which gradually increased in amount until the age of six years, when the patient developed a normal period. Before the age of six, however, there was an abnormal development of secondary sex characters, such as development of the breasts and growth of hair in the axillæ and about the mons. At the age of six the menstrual period was of four days' duration, moderate in amount, regular, occurring at twenty-eight-day intervals. For the next three years, from the age of six to nine, the menses occurred regularly, without variation in amount, duration, or interval. From the age of nine to the present time the amount has been somewhat decreased. At the present time the period is of two days' duration. There never has been dysmenorrhea. During the period the patient is inclined to be somewhat obstinate and perverse. In regard to physical growth and development, the mother states that there was slight abnormal fulness and increased width of the hips before the age of three or four. General development was practically

normal until the age of seven or eight, when disproportion in length of the arm as compared with the torso and leg was noted. At the age of nine her height had not increased more than an inch, and she wore practically the same size of clothing. This peculiarity of development has persisted until the present time, and there is evident definite disproportion between the long and short bone development. The legs and arms are comparatively short, and the torso proportionately long. This disproportion of development and the precocious sexuality constitute the chief complaints. At the age of twelve the patient was placed upon anterior lobe pituitary (Burroughs, Wellcome & Company), and four months later thyroid was added. The subdermal infiltration about the face which was present at that time disappeared under thyroid treatment. There was no other appreciable change. Treatment had been continued until two months ago, without other appreciable response.

Past History.—Pertussis at two years, moderately severe measles at fourteen. *Personal history* unimportant, except fondness for carbohydrate foods. *Family history* unimportant, except tendency of both father and mother to eunuchoidism.

Physical Examination.—Aged fifteen. Weight, 103 pounds. Symphysis to soles of feet, 26½ inches (67 cm.); symphysis to vertex, 30 inches (76 cm.); span, 59 inches (149¾ cm.). General development short, stocky. Hands small, palms broad, fingers proportionately short, tapering, lunular markings not visible (but no overgrowth of perionychial tissue). Wrists slender, without cuffing. Feet of same type. Subdermal infiltration about lower extremities. Normal growth of hair about legs and forearms. Some padding on lateral aspects of thighs. Tendency to genu valgum. Definite development of secondary sex characters, in way of pubic and axillary hair; mammary development good. *Regional:* Hair of medium texture, dry; hairline low, tending to meet outer angles of brows, lanugal growth extending to bridge of nose. Eyebrows thick, meeting in midline. Slight high depression of nose. Teeth irregular, with prosthetic appliances in place. Thyroid not palpable. Lungs and heart show no abnormalities. Vascular system

negative. Blood-pressure, 118/75. Abdomen negative. Genitalia show normal growth of pubic hair, labia majora and minora underdeveloped, clitoris and prepuce well developed, vaginal orifice small. Cervix felt through anterior rectal wall, small, but not conical; fundus not definitely outlined. Neurologic examination negative. Striking characteristic about general

Fig. 36.—Hand of Case IV (aged fifteen), showing dense bony structure, presence and good development of all carpal centers, and complete closure of epiphyseal lines of radius, ulna, metacarpals, etc. (that normally does not occur until eighteenth or twentieth year).

examination is marked disproportion in length of torso as compared with extremities; some disproportion between neck and head and torso.

Urine negative, except for faint trace of albumin and few pus and epithelial cells (non-catheterized specimen). *Blood:*

hemoglobin, 89 per cent.; leukocytes, 11,600; erythrocytes, 3,840,000; Wassermann negative. *Sugar tolerance:* Blood sugar after fifteen-hour fast, 0.106 per cent.; one hour later, following ingestion of 1.59 gm. dextrose per kilogram of body weight, 0.230 per cent.; two hours later, 0.207 per cent. *Basal metabolic rate,* —3 per cent.

Transverse view of skull, sella turcica well visualized, anterior and posterior clinoid processes rather closely approximated, no

Fig. 37.—Contrast of normal hand of fifteen-year-old girl, showing normal epiphyseal markings.

excavation or erosion; anteroposterior diameter, 10 mm.; depth, 8 mm. No abnormal shadow in pineal area. *Stereoscopic of chest* shows no important abnormalities, including thymic area. *Radiograph of hand and forearm* shows all carpal bones present, from hamate and capitate (which appear in third year) to pisiform (which appears in twelfth). Heads of metacarpals completely united to body (this union normally occurring at age of twenty). Heads of all phalanges united to body (union normally occurring between ages of eighteen and twenty).

Lower portion of radius united to body (normally uniting at twentieth year). Likewise, lower portion of ulna has been fused (normally occurring at twentieth year). Showing premature ossification throughout. *Plate of pelvis* shows three primary centers, ilium, pubes, and ischium (which unite in Y fashion into the acetabulum at puberty), already united. Other epiphyses (which appear at puberty and unite at main body of bone at twenty-fifth year) have already united, showing premature ossification of pelvis. *Plate of femur:* Head (which unites at body normally at eighteenth year) shows complete union, no epiphyseal line visible. Greater trochanter (which appears at fourth year and unites at eighteenth) has already united. Lesser trochanter (which appears at thirteenth year and joins body at eighteenth) has already been united. Lower condyles have united to body of femur (union normally occurring at age of twenty). Showing premature epiphyseal closure. *Fluoroscopic examination of head and chest* shows no abnormality except increased thickening and density of short bones.

Electrocardiographic examination shows faint suggestion of right ventricular preponderance.

Adrenalin (Goetsch) test ($7\frac{1}{2}$ minims of 1 : 1000 solution) shows increase in systolic pressure from 110 to 125, with typical secondary fall and rise. Diastolic pressure shows moderate increase from 50 to 55, and at end of fifteen minutes depression to 35, which persists throughout the hour. Pulse shows initial drop from 90 to 80, with later rise again to 90. *Pituitrin test,* 1 c.c. of pituitrin (0), shows moderate depression of systolic pressure, from 125 to 115, and elevation of diastolic from 60 to 75, but no appreciable change in pulse-rate.

Discussion.—In this case the precocious sexual development, particularly menstruation, and the premature ossification and epiphyseal closure suggest hyperovarianism, although no tumefaction was demonstrable. The absence of masculinity and the early menses speak against adrenal participation. The normal or, rather, better than normal mentality is the only feature speaking against hypergonadism and for pineal involvement; although the premature ossification and epiphyseal closure and

the absence of intracranial symptomatology incline one to disregard the pineal as a significant etiology.

In summary, then, the above 4 cases showing precocious puberty seem to be of the hypergonad type, with the possible exception of Case II, whose epilepsy might suggest intracranial symptomatology, and Case I, who has suggestive features of an associated adrenal involvement. It is probably very difficult to assign this most interesting clinical condition to the involvement of any one gland alone, for unquestionably there is a complex reciprocal involvement. In most of these cases there have likewise been secondary signs of pituitary and thyroid disturbance, and there is no logical reason why hyperactivity of the anterior lobe pituitary alone, occurring before adolescence, should not produce precocious sexual development; although, of course, if the anterior lobe pituitary were the sole factor, there should be an associated gigantism.

Conclusions.—The most common etiologic factor in pubertas præcox is hypergonadism, with the adrenal cortex and the pineal next in frequency. In the *male* this sexual precocity may be produced by neoplasm and hyperplasia of the *testes*, *suprarenal cortex*, and *pineal*. In the *female*, most cases of sexual precocity are due to hyperovarianism, rarely to the pineal; and it is probable that most cases of sexual precocity attributed to the adrenal cortex have been really cases of *masculinity* rather than true feminine precocity, this masculinity being manifested by the hypertrichosis, male cast of countenance, mustache, beard, hypertrophied clitoris, etc., without the appearance of true feminine secondary sex characters or precocious menses.

In regard to treatment, if the condition be one of hypersecretion, the logical procedure should be, in the case of tumor, surgery, and in the case of hyperplasia or hyperactivity, in the absence of demonstrable tumefaction, properly directed radiation or suitable antagonistic endocrine therapy.

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CLINIC OF DR. HORACE W. SOPER

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DYSPEPSIA

The term "dyspepsia" in its narrow sense implies a functional gastric disturbance traceable to disorders in the nervous system. A broader application of the term covers the motor disturbances occurring in the stomach regardless of the primary cause. Modern physiologic researches, particularly the work of Cannon,[1] Meltzer,[2] Carlson,[3] and Alvarez,[4] confirm the opinion that nearly all gastro-intestinal symptomatology is based on disturbances in motility. The work of Johnson and Hurst,[5] confirmed by Carlson, demonstrated that the mucosa of the gastro-intestinal tract was devoid of pain nerve endings. The term "hyperesthesia gastrica" is, therefore, untenable. Carlson demonstrated that the pain in ulcer and colic was due to contractions; Alvarez showed that a definite gradient of irritability existed, beginning at the cardia and ending at the pylorus. Briefly, then, we may visualize the gastro-intestinal tract of a normal individual as a beautiful machine timed to a nicety, so that appropriate chemical changes occur concomitantly with the various motor phenomena. The motor processes under the control of the autonomic nervous system proceed without being registered in the consciousness of the individual. He becomes conscious of disturbances when the normal rhythm is interrupted by some inhibitory factor originating in the central nervous system, in the tract itself, or in some distant organ.

We shall, therefore, apply the generic term "dyspepsia" to the group of symptoms produced by inhibiting agents, excluding, of course, gastric and duodenal ulcer, carcinoma, and

other new growths, as well as inflammatory processes and primary secretory disturbances. Clinically the dyspepsia syndrome may be produced by a large number of etiologic factors, and while the general symptomatology is essentially the same, no matter what the underlying cause, we are already able to distinguish certain fairly definite types, such as appendical dyspepsia, gall-bladder dyspepsia, psychic dyspepsia, and so on.

The diagnosis of dyspepsia is difficult and must be established by a process of exclusion. In no department of clinical medicine is a *complete examination* more essential. The usual symptoms of dyspepsia are pressure, distention, belching of gas, eructations of food, nausea, vomiting, anorexia, or capricious appetite.

A series of case report abstracts will best illustrate the various types of dyspepsia.

Case I. Dyspepsia Nervosa.—Male, aged forty-five years. The patient by exclusion is free from any evidence of organic disease. While he belongs to the class that we designate as "sensitive individuals," he is, in reality, sound nervously. He is not emotional and has no psychic disturbances. Is well nourished despite his stomach trouble. His chief symptoms are bloating and belching gas. He is always seeking some new remedy to help get this gas off his stomach, feeling if he did so he would be a well man. He has run the gamut of patent and proprietary medicines. His trouble dates from an attack of acute indigestion caused by eating inordinately of some particular food. Since that time his attention has been focused on his digestive tract. He has excluded many foods, such as pastries, fried food, etc., but manages to consume enough food to maintain a good state of nutrition. He is not constipated, but has formed the habit of taking purgatives to get rid of his gas. Very definite indications for treatment exist.

First: He must be convinced that he has no organic disease and that he has a good digestive power.

Second: He must be informed that gas is a natural resultant

of the digestive process and must not be belched, but must be let alone.

Third: His diet must be definitely prescribed, consisting of easily digested, nutritious, well-cooked food. Additions are gradually made to this diet list until he has succeeded in controlling his belching, and a good general rational dietary has been reached. Cases of this class are not to be mistaken for aërophagia, which differs, inasmuch as aërophagia is a definite primary gastric neurosis and should not be classified as dyspepsia. Some gas is, of course, swallowed in the ordinary act of belching, but is to be distinguished from genuine aërophagia, as emphasized recently by Alvarez.

Case II. Atonic Dyspepsia.—Female, single, aged thirty years. She belongs essentially to the type described by Mills as the asthenic habitus. *x*-Ray examination shows no evidence of organic disease. Motility is slow, but is within the normal limits for her type. Gastro-intestinal tonus is poor. A splash is elicited over the entire epigastrium. The gastric chemistry is normal. Sigmoidoscopy reveals a relaxed atonic rectum and pelvic colon. The rectosigmoid apparatus contracts feebly. Her symptoms are much the same as in Case I, except that loss of appetite exists, and she has omitted so many articles of food from her dietary that she is undernourished and shows evidence of weight loss and general malnutrition. Furthermore, she suffers from extreme lassitude and fatigue. This is the ideal type of case for rest cure. She has been through several very thorough cures, always with benefit, but, unfortunately, her little store of fat quickly melts away when she resumes the usual activities of her life. Treatment must rest on a broader basis than the rest cure. Analysis of her mode of life develops 100 per cent. activity based on 50 per cent. efficiency. She is inadequate, beaten before she starts in the race. She must be brought to a realization of her inability to continue the struggle and taught to live within her limitations. Sufficient food must be taken, even if forced. The first meal of the day should consist of one cereal, inasmuch as such a meal leaves the stomach more quickly than

the mixed meals. Rest and exercise must be so adjusted that each day will show a balance of conserved energy. The detailed management of such a case is obviously difficult, but is amply recompensed by the result secured. Many such patients are now enjoying pleasant, agreeable, useful lives, even if limited in social and domestic activity.

Case III. Psychic Dyspepsia.—Female, married, aged forty years. Exhaustive examination shows no evidence of organic disease. She is well nourished, plump; of sthenic habitus. Her anxious husband accompanies her to the doctor's office. She has terrible spells with her stomach, and gives a dramatic recital of blowing up suddenly with terrific attacks of epigastric pain, belching gas, bloating, and cardiac palpitation. Analysis of her symptoms discloses that the "pain" is really a distended feeling, "as if she were going to die." The attacks rarely last more than one day or night. In the interim she is free from abdominal distress, eats well, without food discrimination. The attacks have recently become more frequent, "when anything goes wrong she has a spell." Obviously she has overworked the nervous fit as a weapon to win domestic battles. She must be told that the attacks are purely of nervous origin, and must be brought under control of the will, that the nervous system may suffer real permanent injury if further indulged in, etc. A therapeutic hint to the doctor who is called during the attack may not be amiss. A hypodermic of $\frac{1}{10}$ grain of apomorphin will cause the attack to cease suddenly. Fear of a repetition of the dose will often act as a wholesome inhibitory factor in the prevention of further attacks.

Case IV. Vagotonic Dyspepsia.—Female, single, aged twenty-five years, has always been nervous, restless, excitable, and energetic. She shows evidence of weight loss. Presents no evidence of organic disease. She complains of bloated feeling after eating, belching gas, heart beats rapidly, often irregularly. Is conscious of pulsation in the epigastrium, often feels as if she cannot secure a deep breath, face often flushed, perspires easily, hands

often cold and clammy. She does not sleep soundly, awakes often with heart pounding, frequently disturbed by dreams. Her thyroid gland is not palpable; there is no fine tremor of the fingers; no eye symptoms of hyperthyroidism. Her basal metabolism is well within the normal limits.

Treatment.—She is given a diet list of well-cooked nutritious foods, excluding tea, coffee, and cocoa. She must have several definite periods of rest, lasting from one-half to one hour each day. Most patients of this type rest better leaning back in a chair than lying down. She must lead a very quiet life, avoiding all excitement. Small doses of atropin help these patients, but we have found that a combination of veronal and atropin is extremely efficacious. A capsule consisting of 1 grain of veronal and $\frac{1}{300}$ grain of atropin is given before each meal. In the beginning one capsule may be given every three hours. The patient rests better and sleeps longer periods at night. This medication is really specific in character. It must be persisted in for months. It is not habit producing and is free from the unpleasant after-affects of larger doses. The intelligent patient soon learns when to stop it and when to resume it.

Case V. Gall-bladder Dyspepsia.—Female, aged fifty years. She has had stomach trouble for a long time and has secured no relief. Has tried various cures and systems of dieting. The time or character of food taken has little or no influence on her symptoms. The chief complaint is a dull gnawing pain in the pit of the stomach. Often feels as if a lump was present in the stomach. Belches gas and eructates sour liquid. The pain is never severe, but is annoying and depressing, frequently awakens her at night. Is usually relieved by a hot-water bag. It is to be noted that in the above list of symptoms there is an absence of the classic symptoms of gall-stone attacks, that is, severe pains coming in attacks radiating to the back and right shoulder, with complete relief from symptoms between the attacks. There is a tendency to constipation. The stomach contents after test-meal are usually subacid and contain an excess of mucus. The duodenal contents by the Lyon-Meltzer

method do not give evidence of any infectious process. *x*-Ray of the gastro-intestinal tract shows rather slow gastric motility for the type of habitus, otherwise nothing abnormal. Gall-bladder plates are negative.

Treatment.—Surgery is to be recommended as the only method of treatment. Dietary and medicinal measures, including drainage by the Lyon-Meltzer method, are useless. Gall-stones are not usually found at operation. As a rule the findings consist of dense adhesions and a definitely pathologic gall-bladder. Cholecystectomy produces prompt permanent relief.

Case VI. Appendical Dyspepsia.—Male, aged twenty-five years, complains of disturbed digestion. Feels bloated, belches, has much intestinal gas, bowels do not act completely. Has sense of uneasiness and distention in right lower quadrant. Vigorous exercise accentuates the symptoms, even to the extent of a feeling of general abdominal soreness. Jolting, such as riding in a car over rough roads, causes abdominal discomfort. Has never had any attacks of acute pain. Purgative drugs give no relief from the symptoms, in fact, usually increase the discomfort. *x*-Ray of the gastro-intestinal tract may result in visualization of the appendix, which does not seem to be structurally abnormal. It may be somewhat dilated. Tenderness to pressure is not marked. In the majority of such cases Mills has observed that the appendix is retrocecal. Gastric motility is likely to be slower than the normal for the bodily habitus of the individual. Gastric acidity findings are subject to the usual normal variations. Treatment is, of course, surgical. Operation is followed by cessation of the gastro-intestinal symptoms.

Case VII. Constipation Dyspepsia.—Male, aged forty-five years, of sthenic habitus. Has been subject to constipation for years. Has tried various drugs and enemata of water. He complains of general digestive disturbances coming on in quite frequent attacks. Has bad taste in mouth, especially in the morning, breath gets foul, loses appetite, belches gas, and feels distended. Has dull headaches and is nauseated. A brisk

cathartic will clear up all the above symptoms, but he hesitates to use active purgatives because they are followed by pain in left lower quadrant and often by cramp-like pains generally distributed about the abdomen. Enemata of water will frequently cause quite severe lower left quadrant pain without being effective in removing much fecal matter; a few small hard fecal "marbles" are passed. *x*-Ray of the gastro-intestinal tract reveals a spastic condition of the iliac and pelvic colon, with diverticula in the descending and transverse colon. It also reveals a relative stasis in the small intestine which can be diagnosticated roentgenologically. Dr. Mills, who demonstrated this condition, terms it "intestinal recoil."

In the class of cases that we are now considering (spastic constipation) the obvious deduction is that the spasm in the lower colon produces a partial obstruction, the effects of which are transmitted throughout the small intestine. Mills'[6] work affords a rational explanation of the symptomatology as above described.

Sigmoidoscopy confirms the *x*-ray diagnosis of spastic colon. The rectosigmoid apparatus is in a state of strong spasmodic contractures, so tight that it will admit no instrument. Treatment consists in the restoration of colonic function along the lines detailed in my article in the St. Louis number of the Medical Clinics of North America (November, 1920). The gastric as well as the general symptoms subside when this restoration is accomplished.

The above described types of dyspepsia are encountered quite frequently. Others are met with which present variations that render them more obscure and difficult to diagnosticate. Organic disease occurring in a nervous dyspeptic clouds the clinical picture. His reaction will be different from that of the phlegmatic individual with chronic appendicitis or gall-bladder disease.

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CLINIC OF DR. BORDEN S. VEEDER

(Post-graduate Clinic at Washington University Medical School)

THE USE OF LACTIC ACID MILK (WHOLE BUTTERMILK) IN INFANT FEEDING OVER LONG PERIODS

Acid milks (whole or low fat buttermilk) have been used in infant feeding for many generations. Many of the writers of a half-century ago and more mention its use, and today we find it discussed briefly, as a rule, in nearly every text-book on pediatrics. It has found its chief use in the form of a low fat or fat-free buttermilk combined with a high carbohydrate, and a much used formula is one containing considerable flour. In the last few years the use of a culturally soured milk (lactic acid milk) has met with considerable success, and this either in the form of a whole soured milk or a skimmed milk, or the two combined. To this acid milk it has been possible to add a high percentage of carbohydrate in some form, as combinations of dextrin and maltose or cane-sugar or commercial corn syrup, and in this way to give infants a food of high caloric value (up to between 75 and 100 calories per pound of body weight) without causing an acute gastro-intestinal upset.

Some fifteen years ago when studying pediatrics I was taught that buttermilk often served as a very satisfactory temporary food, but that it could not be used over a long period of time. This same statement occurs today in one form or another in nearly every text-book on pediatrics and infant feeding. The only reason I have found advanced for this idea was a statement in one book that the infants soon tired of the sour milk. I am quite convinced that this "temporary food" idea is largely a matter of tradition or theory, and, like so many other statements in text-books, is not based upon actual experiences of the

author. I accepted this teaching, like most others, and up until a couple of years ago attempted to change back to sweet milk as soon as the baby had started to thrive on the buttermilk formula. A few babies becoming upset in the attempt to change to sweet milk led to the continuing of the acid milk. As these infants continued to thrive and take the sour mixture with apparent relish, I gradually increased the length of time the acid milk was used, until now I have a series of between 25 and 30 cases in which acid milk has been used continuously for from four to eight or even ten months. This does not sound like a large series of cases, yet when it is taken into consideration that the lactic acid milk is not used routinely, but has only been started to meet some special indication as a severe atrophy, failure to thrive on ordinary formula, gastro-enteritis, etc., it is seen that the series represents a group of "difficult feeding" cases which in these days are becoming more and more infrequent. So far I have not run across an infant who would not take lactic acid milk, nor has it been my experience that they tire of the formula. Furthermore, I have been impressed not only by the steady and even remarkable gain made by the infants fed on acid milk, but in the splendid way they have developed physically. My impression is that they are stronger and more muscular than the infant fed on sweet milk mixtures; that the infant is sturdier. In addition to the acid milk the babies have received cod-liver oil in small doses and fresh fruit juice daily, as is routine for all bottle-fed infants. Between the fifth and sixth month cereal in the form of farina or Cream of Wheat is added, and from four to six weeks later a green vegetable. In St. Louis several dairies have put a culturally soured milk on the market, and I have found these as satisfactory as the milk soured at home. It is simple to make at home, however. My instruction to the mother or nurse is to take a quart of fresh milk, boil hard for several minutes, and then cool rapidly under running water to room temperature. Pour it into a boiled glass jar and add the culture which I bring them from a laboratory. The milk then stands until the following morning at room temperature, and is then beaten up and the day's formula pre-

pared. The next day 3 to 4 ounces of the milk of the previous day is added in place of the culture. For carbohydrate corn syrup or dextromaltose has been used as a rule. It is my experience that infants will take the acid milk at once and continue to relish it for months.

The following histories, illustrated by graphs, are examples of the long-continued use of lactic acid milk (whole buttermilk), and show what may be considered as indications for its use. This last I mention because it is frequently asked by the postgraduate students. Briefly the indications are these: If I run across an infant over two months of age who has been off the breast for two or more weeks and who is not only 3 to 4 pounds under average weight for the age, but markedly undernourished and marantic, I believe in starting at once with acid milk. Second, if a baby has been doing well on the breast or a complemental feeding, and then will not adjust in three weeks to a sweet milk mixture after breast feeding has been stopped, I turn to acid milk. These points are brought out in the case histories.

Case I.—Baby H. This baby was brought to me when three months of age and presented a picture of severe malnutrition with enlarged spleen and anemia. The birth weight was 7½ pounds, and the baby had been fed in turn on the breast, condensed milk, and finally on a sweet milk formula. There had always been considerable colic and persistent loose stools, along with the failure to gain weight and thrive. At three months the weight was 8 pounds, or 4 pounds under the average age weight. Because of the severe malnutrition and the time of year (July) the baby was at once placed on whole lactic acid milk with carbohydrate in the form of corn syrup, with a caloric value of 74 calories per pound. The baby started in to gain at once (Fig. 38). In four months, or by the time the baby was seven months, the average weight line was reached, the average gain being over 2 pounds per month during this period. Cereal and vegetables were added as indicated on the chart. The lactic acid milk was continued in increasing strength from the third to the eighth month, or over a period of five months, and then a

gradual change made to sweet milk without difficulty or interruption in the weight curve. As the baby gained weight the spleen became smaller, and the baby became strong and mus-

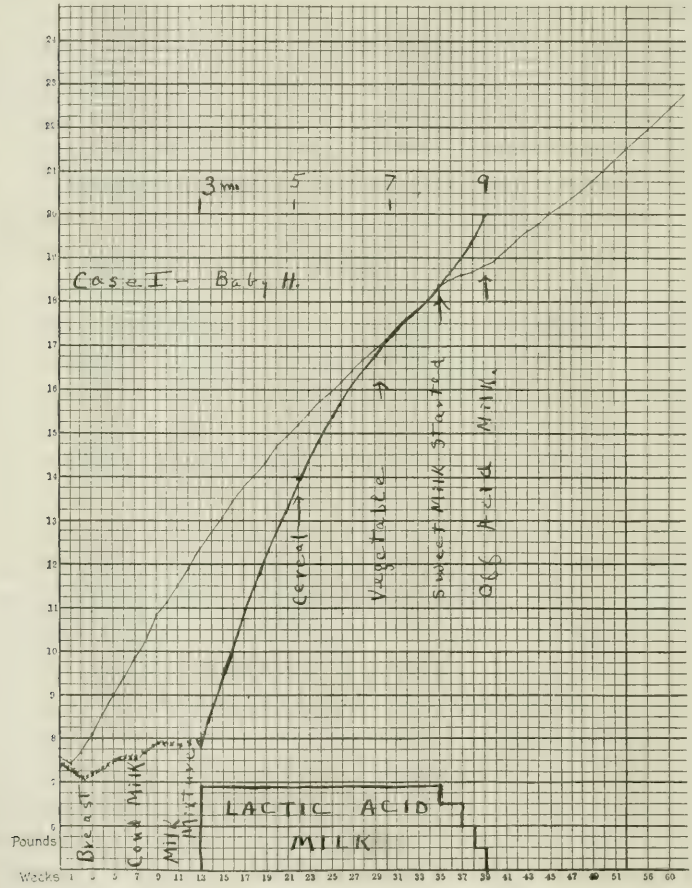

Fig. 38.—Baby H. Severe malnutrition. Whole lactic acid milk for six months.

cular and was walking about by the eleventh month. Cod-liver oil was started at the same time as the lactic acid milk, and my record notes that all traces of malnutrition had disappeared by the sixth month.

Case II.—Baby Si. In this case acid milk was used continuously over a period of eight months; from the second to the eighth month exclusively and then for one month in combina-

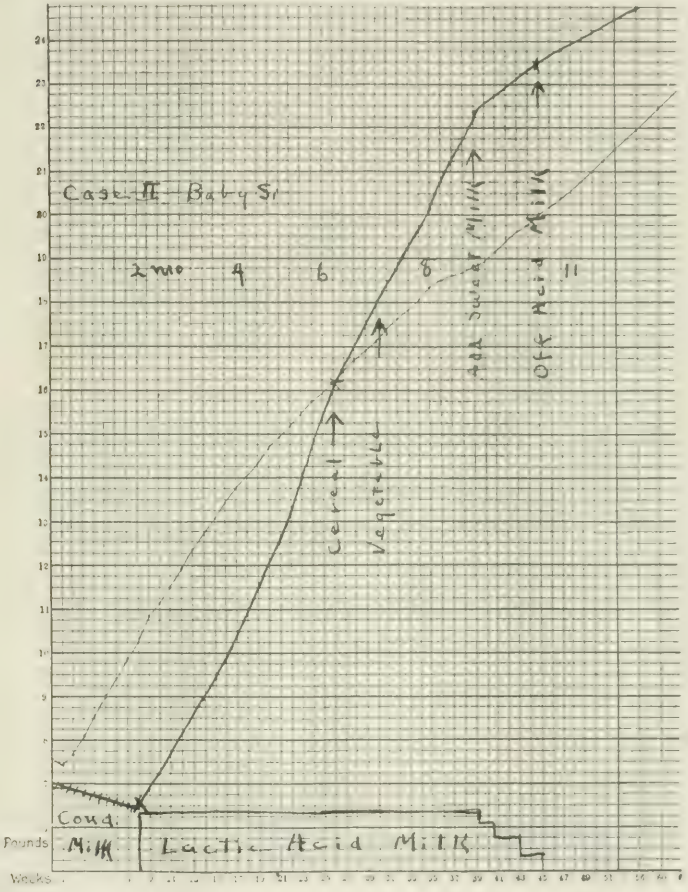

Fig. 39.—Baby Si. Severe malnutrition. Whole lactic acid milk for eight months.

tion with sweet milk. The baby was brought to the Infant Welfare Clinic when two months of age in a severe state of malnutrition and with sore, excoriated buttocks. At this time (eight weeks) it weighed 6½ pounds. Very little could be ascertained

of the early history, as the mother had died when the baby was thirteen days old. The exact birth weight was unknown, but was said to be "about 7 pounds." Since birth the baby had been fed on condensed milk, and for two weeks previous to admission on a milk formula of low caloric value with a high percentage of carbohydrate. The baby was started at once on a lactic acid formula of about 60 calories per pound, and in the first two weeks gained 14 ounces. The formula was gradually increased until at four months the baby was receiving 65 calories per pound. In four months (Fig. 39), or when the baby was six months of age, the average weight line had been reached. Cereal was then added, and later vegetables, and at nine months, when the change to sweet milk was started, the baby weighed over 22½ pounds, having gained 16 pounds in seven months on a lactic acid milk formula.

Case III.—Baby L. This case was an interesting problem, as a moderately severe degree of malnutrition was associated with severe rumination. The baby was born in California and weighed 7¾ pounds at birth. It was breast fed for two weeks and then put on dry milk powder. It did fairly well on this at first until a bad intestinal upset occurred as a result of a "rancid can." About this same time persistent vomiting developed, and it was thought by the local physician that the infant had a pyloric stenosis. When about two and a half months of age the baby was taken to Dr. Lucas in San Francisco, when the baby was transfused and put on breast milk complemented with skimmed lactic acid milk. After three weeks in the hospital the baby was brought home to St. Louis, making the journey on skimmed acid milk. At three and a half months the baby weighed 10 pounds, or 3 pounds below average weight for age. The tissues were soft and flabby and the infant might be classed as in a state of moderately severe malnutrition. The factor dominating the picture was the marked rumination. A whole lactic acid formula of high caloric value was started, and while the infant took all his food, he was unable to retain enough to gain because of the rumination and spitting. The baby was

then given a pacifier immediately after each bottle in order to have something besides his food to chew, and at once the weight curve started up. From this time on the gain was rapid, and at eight months the average weight was reached. Counting

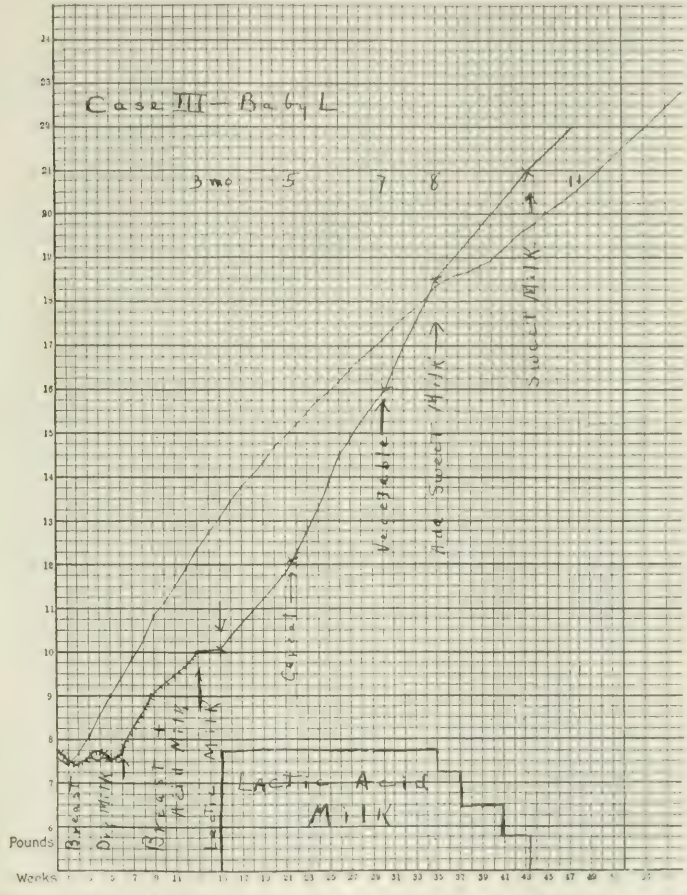

Fig. 40.—Baby L. Rumination. Whole lactic acid milk for six months.

in the period before arriving in St. Louis this infant was on lactic acid milk for a period of seven months. Figure 40 shows the rapid gain in weight. Cod-liver oil was used continuously. It was necessary to continue the use of the pacifier for a period of several months.

Case IV.—Baby S. In this case lactic acid milk was used from the second to the eighth month—a period of six months. The baby had been breast fed one week and then adopted.

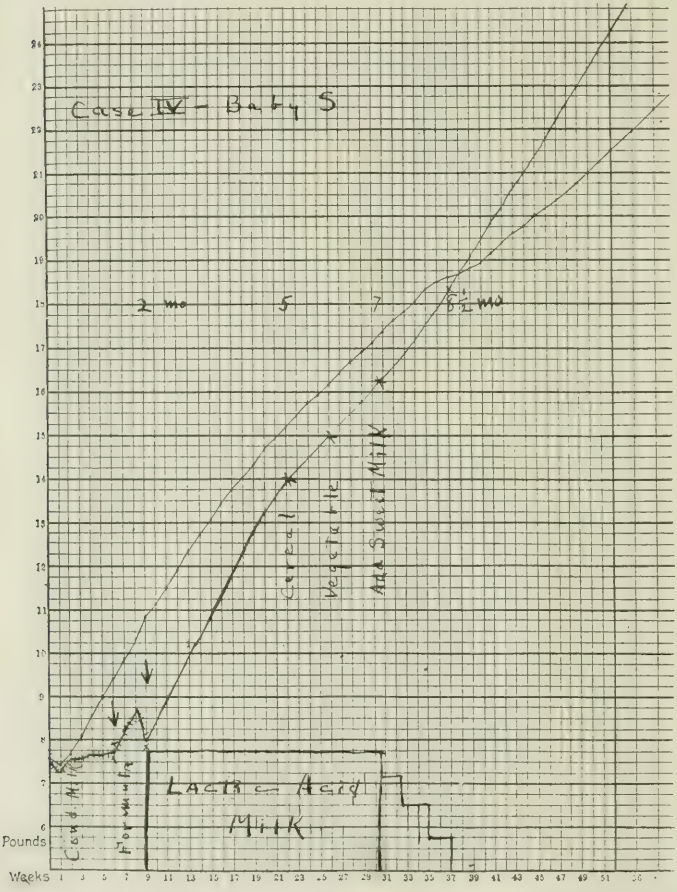

Fig. 41.—Baby S. Malnutrition. Failure to thrive on sweet milk formula. Whole lactic acid milk for six months.

The foster parents had first tried condensed milk, and then, in turn, a milk formula, and finally Thompson's Patent Food. It was decidedly undernourished when I first saw it at two months of age. At birth it had weighed $7\frac{1}{2}$ pounds and at six weeks $7\frac{3}{4}$

pounds. Not only was the skin dry, but showed numerous small boils. A sweet milk formula was tried for three weeks. For two weeks the baby gained, but then lost as a result of diarrhea. So at nine weeks, when the baby weighed 8 pounds, a change was made to whole acid milk. Figure 41 shows the immediate rapid gain and how it continued, the average weight line being reached at eight and a half months. This case, one of the earliest in the series, also shows the satisfactory progress made by the infant after it was changed over to a sweet milk formula.

Case V.—Baby E. This case illustrates the change to lactic acid milk as a result of failure to change satisfactorily from breast milk to a sweet milk formula, together with the use of the acid milk for a period of six months. In this case there was no athrepsia or malnutrition, and the baby had made very good progress for the first two months. The baby had received breast milk for six weeks and then complemental feeding for three weeks. When the attempt was made to give a diluted milk formula alone the baby started to vomit as soon as the mixture was of sufficient strength to furnish enough calories for gain. After three weeks' trial, with failure to gain or improve, a change was made to lactic acid milk, and immediately the baby started to thrive (Fig. 42). The lactic acid milk was continued and cereal and vegetable added as noted on the graph.

Case VI.—Baby Sc. This baby was another case at the Infant Welfare Center. It was brought to the conference when two and a half months of age with a severe degree of malnutrition, and at this time was some 5 pounds under the average weight for age. Very little was ascertained of the early history. It was said to have been about 7 pounds at birth, and when brought to the clinic weighed 6½ pounds. It had never been on the breast, but had been fed condensed milk irregularly. The baby was placed on a lactic acid milk with corn syrup at a strength of about 75 calories per pound of body weight. The infant is now ten months of age and is still on lactic acid milk. The weight curve in this case has not reached the average line.

but parallels it almost exactly since the acid milk was started. The baby has received the lactic acid milk continuously for a period of eight months, and today is strong and well developed

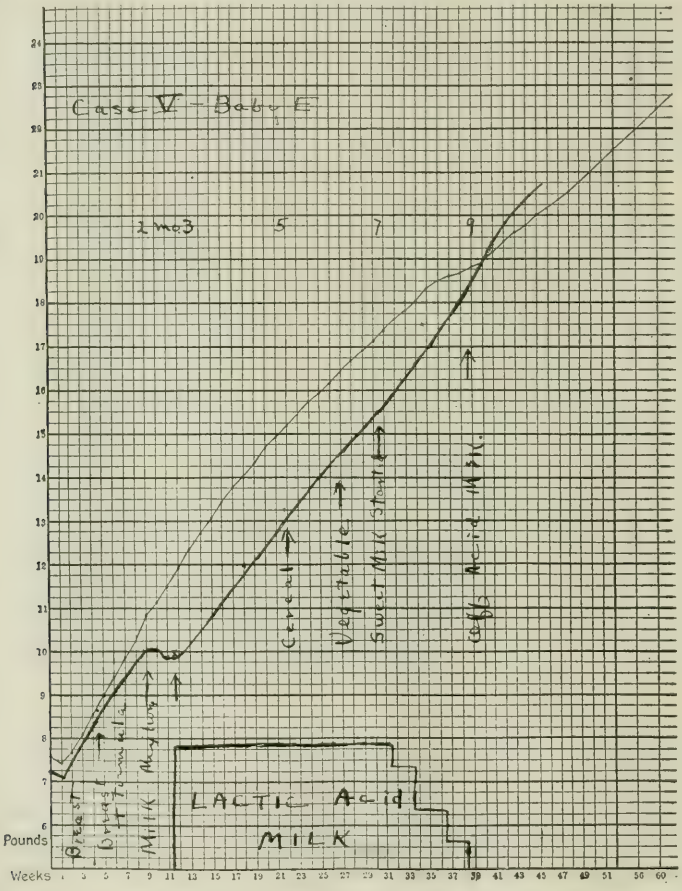

Fig. 42.—Baby E. Failure to adapt to sweet milk following removal from breast. Whole lactic acid milk for six months.

and shows but little trace of the early malnutrition. Sweet milk will now be started.

These 6 cases are sufficient I think to illustrate my point —that it is possible to feed a young infant on an acid milk over

a long period of time and have the infant not only take and relish the formula, but gain and thrive in as satisfactory a manner as could be desired. Incidentally they illustrate the value

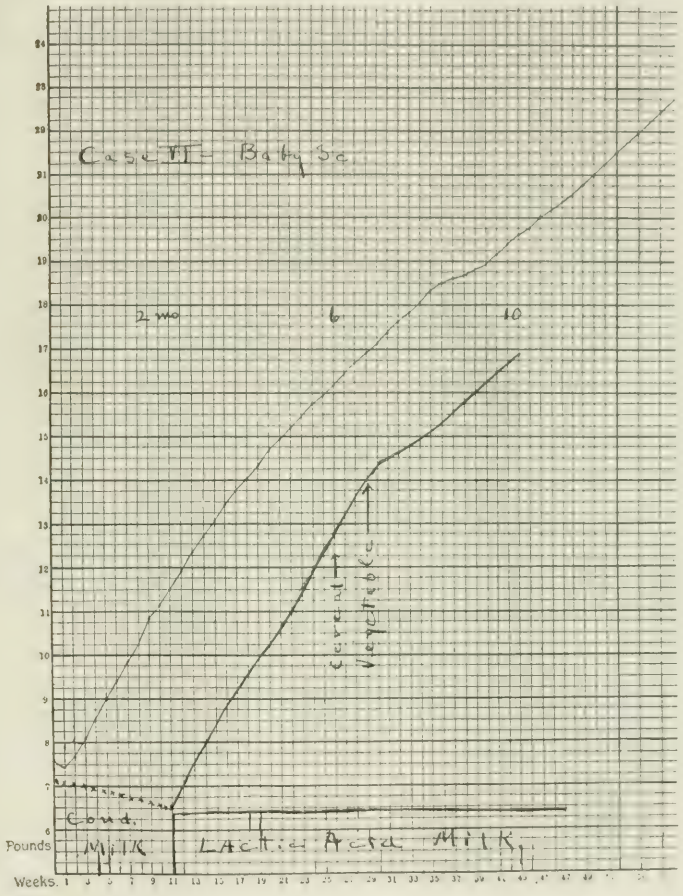

Fig. 43.—Baby Sc. Severe malnutrition. Whole lactic acid milk for eight months.

of acid milk in cases of malnutrition, a point perhaps even more important, but not the point we are discussing at the present moment. Before an undernourished infant can be expected to gain or thrive it must receive a food of the caloric

value required by the average weight infant of the same age. Acid milk mixture, or buttermilk with high carbohydrate, gives us a food of this type which the infant can handle, and, as these cases show, this food can be continued over periods of months.

The point may well be raised, and I have asked it of myself a number of times, if the infants do so well, why should not acid milk be used routinely as an artificial food rather than sweet milk? As stated, I have used it only when there has been some special indication, as marasmus or failure to adjust to sweet milk after a sufficient trial. There is no objection except that it is unnecessary in the vast majority of artificially fed infants, and the difficulty with acid milk in the home is the parental feeling against "sour milk." A mother with a malnourished colicky baby will try anything, but the mother with a strong healthy infant will object strenuously to feeding her baby sour milk. In these cases the change to sweet milk has been made from the ninth to the twelfth month. There has been no particular reason for the change at this time except one of convenience, and, in fact, several mothers have objected vigorously to the change after the way their infants have developed on acid milk from puny atrophic infants to normal strong babies, often over average weight, as the charts show.

My contention is this—that in my experience, contrary to the usual view presented in texts on infant feeding, buttermilk containing fat or whole lactic acid milk is a very satisfactory and unobjectionable food for the use of infants over periods of months.

CLINIC OF DR. LOUIS HENRY HEMPELMANN

EVANGELICAL DEACONESS HOSPITAL

TREATMENT OF PERNICIOUS ANEMIA

I WISH to speak to you today of the use of repeated blood transfusions in pernicious anemia, and to demonstrate 2 patients who have been under treatment a sufficiently long time to make their histories interesting. Before presenting these cases it will probably be wise to say a few words about pernicious anemia in general and the use of blood transfusions in this disease.

The subject of pernicious anemia is still in a very unsettled state; the etiology is obscure, the course of the disease is variable, and the treatment is unsatisfactory at best. There seems to be no cure for the disease, although some cases have remissions lasting five or even ten years, and still eventually succumb to the disease. Hence, it is difficult to judge whether the improvement following any method of treatment is the result of the treatment or is due to a spontaneous remission, but I am sure that cases treated by repeated transfusions feel so much better subjectively and remissions occur so much more frequently in cases treated in this way that blood transfusions offer more real benefit to these unfortunate patients than any other method of treatment. A recent writer says that "transfusions bring about 10 to 20 per cent. more remissions than would occur without same," and that "no patient is too sick to be transfused." This seems to be the consensus of opinion of all who have experience in this line of work. It must also be remembered that prolonged anemia is detrimental *per se* to all the organs of the body, and that it is, therefore, not wise to wait

until the red blood-cells and hemoglobin are too low before resorting to transfusion if one would avoid irreparable damage. Splenectomy seems to offer about the same benefit as can be derived from a transfusion, and the results following splenectomy in most cases are not any more permanent than those following simple transfusion. The influence of foci of infection in pernicious anemia is still a debatable question. Very probably they play a rôle in its etiology, and it is, therefore, wise to make a diligent search for such foci and remove them whenever possible. Frank Smithies, of Chicago, believes that in most cases of pernicious anemia the gall-bladder and appendix are foci of infection, and he has reported a large series of cases in which the removal of these organs together with removal of the spleen was carried out. Transfusions were given these cases before and after operation, with great benefit. It is, perhaps, a little too early to speak of the end-results of this method of treatment; the results, however, seem to be encouraging, provided one can get the patient into sufficiently good shape to be a fair surgical risk and can gain consent to the operation.

While the method of grouping blood, described by Moss in 1910, has made transfusions a safe procedure, and the citrate method, described by Lewissohn in 1915, has made it a practical operation which can be carried out without elaborate paraphernalia in any home by almost anyone, it must be confessed that many problems still remain to be solved before the subject of transfusion can be termed a closed chapter. The occurrence of reactions following transfusions is one of these obscure problems. They are disagreeable and at times dangerous in debilitated persons. Reactions follow transfusion by any method—a little more frequently, it is true, if citrate is used—but the ease with which citrate transfusions are carried out, even in the private home, makes it the operation of choice in my opinion in most cases.

Harold M. Bowcock, in the March number of the Johns Hopkins Bulletin for 1921, under the caption, "Serious Reactions to Repeated Blood Transfusions in Pernicious Anemia," reports 3 cases occurring at the Johns Hopkins Hospital in

which it was thought best to stop blood transfusion because of the severity of the reactions. In Case I, $10\frac{3}{4}$ liters of blood were given in seventeen transfusions during 1915–16. Rather large amounts, 550 to 900 c.c., were administered, and it is worthy of note that on three occasions hemolysis developed, evidently due to incompatibilities which could have probably been avoided at the present day.

In Case II $8\frac{1}{2}$ liters were given in twenty transfusions in 1916. There was no hemoglobinuria, and while the reactions described were decidedly unpleasant, one would hardly feel justified in discontinuing a procedure which was of such great benefit merely because of these reactions.

In Case III $8\frac{1}{2}$ liters were transfused in fifteen operations with some unpleasantly severe reactions, including one hemolysis. He concludes:

"In certain cases of pernicious anemia which have been transfused repeatedly transfusion becomes self-limited because of the inadequacy of methods of selecting suitable donors."

While it is true that these severe reactions are dangerous in these cases, it has been our experience that a patient may have a severe reaction at one transfusion and have only a feeble reaction at the next given a few days later. I would, therefore, urge that this method of treatment be not abandoned without serious deliberation. One should remember that this is virtually the only line of treatment that gives results, and that most of these unfortunates succumb to the disease at any rate within a short time if not transfused. It is, however, advisable to select a new donor for the next transfusion and be very careful about grouping the blood.

Be the cause of the reactions following blood transfusions what it may, I am absolutely sure that the severity of the reaction can be reduced, and in many cases the reaction itself prevented by the hypodermic administration of $\frac{1}{4}$ grain of morphin with $\frac{1}{150}$ grain of atropin during or before the transfusion. Morphin has been used in the past quite extensively to stop the chill in malaria, and atropin has long been recognized to be of service in anaphylactic phenomena. Morphin and atropin,

therefore, seem ideal to combat the unpleasant sequelæ of the transfusion. The reaction following transfusion usually subsides in six to eight hours, and if the patient has been well narcotized during this time he awakens with only a hazy recollection of what followed after the transfusion. As a matter of fact, there is usually very little chill, and while there is frequently a mild fever —100° to 101° F.—the patient, thanks to the morphin, is not uncomfortable during the reaction, and does not dread the next transfusion as is the case if no morphin is used.

It is difficult to decide just how often transfusions should be repeated in pernicious anemia. For financial and other reasons one is usually anxious to get along with as few transfusions as possible, but I believe it is best to make frequent blood counts and to transfuse whenever a decided downward trend of the count is evident. The patients themselves can often tell by their subjective feelings when another transfusion is necessary.

Winifred Ashby, in the Journal of Experimental Medicine, August, 1921, has made a careful study of 33 cases of pernicious anemia in Groups 1, 2, and 3, which have been transfused with Group 4 blood; she finds that the transfused red corpuscles may be identified in the blood-stream as late as one hundred days after a transfusion. The blood destruction in these cases is no more rapid than in normal individuals, and the destruction of the red blood-cells seems to go in cycles which in women are coincident with menstruation. She also questions whether blood destruction is as important a factor in producing the anemia as it is usually assumed to be.

I wish to present 2 cases of pernicious anemia that have been transfused repeatedly with benefit, and to speak of a third case that had been transfused seventy-four times, which died recently.

Case I.—This lady is sixty-eight years of age. The family history is good and the previous history unimportant. She came under observation for a pernicious anemia in 1918. At this time the anemia was not very severe and she was treated by the usual methods until September, 1919, at which time the

red blood-cells had come down to 1,500,000 and the hemoglobin to 40 per cent. Two transfusions at intervals of two weeks brought the count up to 3,400,000 and the hemoglobin to 62 per cent., and she felt relatively well. She was transfused at intervals of several months until September, 1920, at which time a remission set in and she remained in good condition for thirteen and a half months (to October 15, 1921), by which time she began to lose ground. The red blood-corpuscles were 2,120,000 and the hemoglobin 30 per cent.; the white blood-corpuscles, 8000.

She was transfused again, with considerable improvement. This patient has gotten nine transfusions in the past four years. She had quite a severe pyelitis lasting several weeks some fifteen months ago, and withstood a series of chills and fever due to the pyelitis about as well as a normal person. The last transfusions were given on June 17th and July 1st of this year; the first of these was followed by a very severe reaction, but the next was followed by a very mild reaction, showing the variability in the way patients react to transfusions. At present she is only fairly well and the last count made only a few days ago showed red blood-cells 1,950,000; hemoglobin 45 per cent. Subjectively, however, she feels quite well.

Case II.—The next case, a lady forty-seven years of age, came under observation in November, 1917, with a red blood-cell count of 1,800,000 and hemoglobin of 35 per cent. The family and the previous histories are unimportant. She did not do well under the usual treatment and was transfused on November 30, 1917—400 c.c. of blood being injected. There was a very decided improvement following this operation, and she remained in relatively good condition for three months, at which time she began to lose ground. She was then transfused four times at weekly intervals, and after the fourth transfusion the red blood-cells numbered 2,612,000 and the hemoblobin 70 per cent. She seemed a fairly good surgical risk and underwent a splenectomy on May 24, 1918. The spleen was very adherent and its removal was unusually difficult; the patient collapsed

on the table and was rallied only with great difficulty. Following the operation she did very well. The reds went up to 2,500,000 and later to 3,000,000 and the hemoglobin up to 75 per cent. Four weeks after the splenectomy the gall-bladder and appendix were removed. She stood this operation rather better than the splenectomy and returned to her home in three weeks. She felt pretty well for the following three years, although her red count never exceeded 2,500,000 to 3,000,000 and the hemoglobin varied from 40 to 70 per cent. She did not seem to do well during the past summer, and a course of neosalvarsan was then administered, without benefit, after which a transfusion was given in August and another in October of last year. The last transfusion was given on November 3, 1921, at which time the red blood-cells numbered 1,864,000 and the hemoglobin 21 per cent. Since that time she has been relatively well, although the last count showed 2,656,000 red blood-cells and hemoglobin 50 per cent. It is often remarkable how well these patients feel and how much work they are able to do in spite of an anemia such as this lady has. She will probably need more transfusions in the near future. It is worthy of note that she contracted the influenza in 1920, which was followed by an empyema and rib resection, from which she made a perfect recovery.

Case III.—The last case of which I wish to speak, unfortunately, died last April of an intercurrent disease. She came under observation in June, 1918. At that time the red count was 1,520,000, hemoglobin, 22 per cent., and white count 4600; differential: Polymorphs., 61.7 per cent.; large lymphocytes, 3.6 per cent.; small lymphocytes, 25.6 per cent.; mononuclears, 9.2 per cent. Nine nucleated red blood-corpuscles in 250 white blood-cells counted. A transfusion was suggested, but was not accepted, and the case dropped out of observation until January 3, 1919, at which time the red blood count was 1,040,000, hemoglobin, 14 per cent.; she was edematous and said she had been confined to her bed for four months. A transfusion of 400 c.c. of partly defibrinated blood was given, followed by another transfusion of 500 c.c. a week later. This second transfusion

caused a dilatation of the heart with engorgement of the liver and pulse of 140. Happily she rallied under the usual restoratives and felt so much improved that she was able to go out auto riding five days later, or twelve days after the first transfusion. This patient was under constant observation since that time and has been transfused every two to four weeks without having anything which could be spoken of as a definite remission. Last summer she went to Atlantic City and remained at the seashore three weeks, coming back much improved, but declined so rapidly that another transfusion had to be given within a week after her arrival in St. Louis. She lost ground very rapidly when once she began to slip, became peevish, ill-tempered, and showed mild mental symptoms, but rallied almost at once after a transfusion, and seemed like a different person. She had improved so that the last count showed: red blood-cells, 2,696,000; hemoglobin, 64 per cent.; white blood-cells, 4400; differential: Polymorphs., 42 per cent.; large lymphocytes, 4 per cent.; small lymphocytes, 49 per cent.; large mononuclears, 2 per cent.; small mononuclears, 2 per cent.; transitionals, 0; eosinophils, 0; occasional nucleated red.

On April 17, 1922 she had a chill due to a pyelitis. Her resistance was poor, and she became rapidly worse and died in three days. Seventy-four transfusions had been given in this case without the occurrence of especially alarming reactions.

Unfortunately, this case was not a typical addisonian pernicious anemia; the color-index was always below 1, and there were very few nucleated reds. The white count was always low, but she had a good deal of sore mouth and had the occasional digestive upsets which are seen in pernicious anemia, so that I feel justified in including it in this category. It could probably be called an aplastic pernicious anemia. This patient had 37,000 c.c. (approximately 9 gallons) of blood injected into her veins in these seventy-four transfusions.

On going over the literature at my disposal I could find no other case that had been transfused so often.

I have had three mishaps, but, fortunately, no fatalities in doing transfusions. In one case a "one plus" Wassermann in a

donor was ignored with disastrous results, the patient contracting lues. In another case there was a hemolysis after 25 or 30 c.c. of blood was injected. The injection was stopped and the patient recovered. This transfusion was attempted in the country, and the local doctor took the blood from several donors and the patient and sent it in to be grouped. It is quite possible that a mix-up of the bloods occurred and that they were incorrectly labeled, although it must be confessed that hemolysis does occasionally occur in spite of all precautions. The patients grow restless if the donor's blood is incompatible with theirs, complain of intense backache, vomit, and go into collapse after receiving 15 to 25 c.c. of blood. The urine is claret colored at the next voiding. They almost invariably recover if the transfusion is stopped at the appearance of the first untoward symptom and the usual restorative remedies are applied. It is probably best to give the first 50 c.c. of any transfusion slowly because of the possibility of this accident. In the third instance the heart dilated as reported in Case III.

Whenever possible donors should be selected belonging to the same group as the patient, but in many other cases Group 4 blood has been used in patients whose blood was in the other groups, with perfectly satisfactory results. No donor should be used twice for the same patient at more than three-day intervals without a re-examination for isohemolysins and iso-agglutinins. I have usually injected 500 or 600 c.c. of blood at each transfusion, as it seemed better to transfuse repeatedly at short intervals than to use large amounts at infrequent intervals. The transfused blood seems to stimulate the blood-forming organs, as often the increase in red cells following a transfusion of even a small amount of blood is too great to be accounted for by the number of red cells administered in the transfusion.

It is a very great advantage to have a certain number of professional donors already grouped and subject to call for emergency cases. Healthy, robust students answer admirably, and the taking of 500 or 600 c.c. of blood inconveniences these young men very little; in fact, one of our donors played baseball a few hours after giving 500 c.c. of blood for transfusion.

Before concluding I would like to say that we have found transfusions very beneficial to shorten convalescence in anemic cases of gastric and duodenal ulcer, whether treated medically or surgically, also in cases of sepsis and to stop hemorrhage in cases of hemophilia, and in those cases where bleeding occurs following some operation. It has been of only temporary benefit in cases of streptococcus viridans endocarditis.

CLINIC OF DR. W. McKIM MARRIOTT

St. Louis Children's Hospital

CHRONIC DIGESTIVE INSUFFICIENCY (CELIAC DISEASE)

The 2 patients presented today are typical examples of a condition of chronic digestive insufficiency of the type that has been referred to by English authors as "celiac disease." One patient is two and a half years old and the other three. The general appearance of the two children is strikingly similar. They are both pale, emaciated, and stunted in growth. The abdomens are prominent. Both children are irritable and fretful. The weight of the younger one is now 22 pounds. The weight at two years was only 12 pounds. The weight of the older one is now 20 pounds. Three months ago it was 16 pounds. Neither child is taller than an average infant one year of age. Neither is able to walk alone. Both are able to use a few words and the older child to speak in short sentences. The mental development is somewhat retarded, but not nearly to the extent of the physical. Except for the emaciation and the distended abdomen there is nothing abnormal in the physical examination of either child. There is no fever in either case. There is no evidence of tuberculosis; the Wassermann and Pirquet tests are negative. The urines are normal. The blood-picture in each instance has been that of a secondary anemia.

The 2 cases are so similar in every respect that a discussion of one of them will suffice. The younger child (P. B.) was normal at birth, weighing 7 pounds, and was breast fed for the first seven months, and then weaned to a whole milk mixture. At the age of one year he weighed 20 pounds, but at about this time he began to lose weight, and became pale and apathetic.

His stools were numerous, were pale in color, and very foul in odor. The appearance of the stools was similar to that of cooked oatmeal. There was considerable mucus, but no blood or pus.

During the next six months the child lost 6 pounds in weight. During this time he was treated on a variety of diets, and was finally, under the direction of a physician, placed on a protein milk formula, and, in addition, was given vegetable broth and scraped beef.. On this diet diarrhea was less and the child gained in weight slowly for a period of two months. The diarrhea then increased, the stools being watery and frothy. and as numerous as ten and fifteen a day. Considerable loss in weight occurred, the child losing 3 pounds in two weeks. The weight then increased somewhat, although the diarrhea continued. It became evident that the increase in weight was due to edema. At this time the child was brought to the hospital for treatment.

On admission he was very weak and only semiconscious. There was nothing abnormal on physical examination besides the poor state of nutrition and the marked edema. The stools were watery and of foul odor. Under suitable treatment (see below) the diarrhea ceased and the edema disappeared. At this time the child's weight was 12 pounds. His food was gradually increased, and a small gain in weight began, which continued for the next two months. The stools became firm in consistency. The child was discharged from the hospital, and while away during the summer once more developed diarrhea. On account of this he was kept on a very low diet, consisting largely of skimmed lactic acid milk. The nutritional edema reappeared, and a few weeks later the child was again admitted to the hospital in about the same general condition as when first admitted, except that he was more anemic, the red blood-cells being 2,300,000, hemoglobin 45 per cent. The child was given a transfusion of 4 ounces of citrated whole blood, and put on a diet, which will be described below. He showed a fair gain in weight and this gain continued without remission for several months, his weight going as high as 25 pounds. At this time he suffered an attack of influenza, ran a high tempera-

ture for a few days, and developed diarrhea. His weight dropped to 20 pounds, and slowly began to increase. He is now in very good physical condition.

This child showed, in a striking manner, the cardinal symptoms on which the diagnosis of celiac disease is made. These symptoms are emaciation, great fluctuation in weight, protruding abdomen, large foul, soapy stools, and specific intolerance to fat in the food. The condition must be differentiated from abdominal tuberculosis, which may give rise to a somewhat similar symptomatology. In tuberculosis, however, the tuberculin skin tests are usually positive and there is likely to be evidence of intestinal adhesions, free fluid in the abdomen, and enlarged mesenteric glands. Such rapid and marked fluctuations in weight do not occur. Hirschsprung's disease, or megacolon, is also associated with an enlarged abdomen and emaciation. There is, however, in this condition marked constipation and only very rarely diarrhea. The enlarged colon may be palpated and outlined under the fluoroscope. The colon in celiac disease, although moderately distended, does not attain the enormous size encountered in Hirschsprung's disease. A condition of emaciation with enlarged abdomen may be seen in children who have been fed on an unsuitable diet, especially one made up of large amounts of bulky food, and with little fat and protein. The history of the feeding rules out this condition. These patients with celiac disease present such a characteristic symptomatology that the diagnosis is not difficult for anyone who has seen such cases.

In order to properly treat an infant of this type it is necessary to have a clear conception of the nature of the condition. There is not sufficient evidence that the disease is due to an infection. There have been no constant pathologic findings in cases of this kind. The liver may be small, the pancreas occasionally shows slight atrophy, and the intestines may be distended. As far as our present knowledge goes, the condition is a purely functional digestive insufficiency.

During the period that this infant was in poor condition and losing weight examination of the stomach contents, at the

height of digestion, revealed the fact that there was an almost complete absence of hydrochloric acid. Examination of the stools during this same period showed that they consisted largely of soaps, and that the absorption of fat from the food was less than 10 per cent., over 90 per cent. being eliminated in the stools in the form of these soaps. Although fats were very poorly absorbed, the protein of the diet was almost completely digested and absorbed, even when large amounts were given, less than 5 per cent. being lost in the stools. It had been noted before the child came to the hospital that the addition of sugar to the diet led to an almost immediate increase in the number of stools. It would seem that on account of the lack of digestive function fermentable sugars in the intestinal tract were readily broken up by the organisms and with subsequent production of irritating products capable of setting up increased peristalsis. The edema was evidently of the type known as "nutritional" or "war" edema, a condition which has been attributed to lack of the fat-soluble "A" vitamin in the diet.

With these facts in mind as to the nature of the condition the principles of treatment may be outlined. It is necessary to supply these children with a sufficient amount of food to furnish their daily energy requirement. That is to say, there must be sufficient calories. As these children are unable to utilize fat this must be practically eliminated from the diet. No easily fermentable sugar can be added. The bulk of the diet must, therefore, be made up of protein and such forms of carbohydrate as are not readily fermentable. Furthermore, the food given must be one which does not tend to neutralize the slight amount of gastric hydrochloric acid. It is also essential that the three vitamins, fat-soluble "A," water-soluble "B," and the anti-scorbutic substance be supplied. Also a certain amount of iron and pigment are necessary for the production of blood.

The basis for the diet of this infant is skimmed lactic acid milk (buttermilk). This contains practically no fat, a relatively small amount of sugar, considerable protein, the necessary mineral salts, and a fair amount of water-soluble vitamin. On account of the lactic acid present it does not neutralize the

gastric juice to nearly the extent that sweet milk does. One quart of this skimmed lactic milk is given in the course of a day, but this does not supply a sufficient amount of food. Additional food may be added in the form of milk protein. In order to accomplish this the curds from skimmed milk may be used or one of the forms of dried casein (larosan, casec, etc.). In the case of this infant the curds from 3 quarts of skimmed milk, or 3 ounces of dried casein, were added to the day's feeding. The fat-soluble "A" vitamin must be supplied, and as these infants can take very little fat it is difficult to administer this vitamin, which always occurs in association with fat. Cod-liver oil is extremely rich in this vitamin, so that a small amount of the oil contains as much as a great deal of butter fat; 1 or 2 teaspoonfuls of cod-liver oil in the course of a day supplies a sufficient amount of fat-soluble "A" vitamin and yet is not a sufficient amount of fat to disturb the digestion. The cod-liver oil is ground up with the curds or casein, and the whole mixed with the skimmed lactic acid milk and passed through a sieve. In order to supply iron and pigment and also an additional amount of water-soluble "B" vitamin, 2 or 3 teaspoonfuls of powdered spinach boiled in a small amount of water is added to the milk mixture. To supply the antiscorbutic vitamin 1 tablespoonful of orange juice is given daily.

Additional protein is also supplied in the form of rare scraped beef, 1 or 2 teaspoonfuls a day. Recently one-half of a soft-boiled egg has been given once a day, taking place of one of the meat feedings. Moderate amounts of starch may be digested by these infants. Suitable forms of starch are well-cooked farina, Cream of Wheat, or baked potato. It is stated that some infants do not tolerate potato well, but this has not been our experience. To supply additional calories a difficultly fermentable form of sugar may be used. The most suitable form for this purpose may be the commercial dextrin or the ordinary brown corn syrup. From ½ ounce to 3 ounces of either of these may be added to the milk mixture. Such a diet as that outlined supplies every need for nutrition and is a diet on which this child has been fed. The other child has been fed on the same diet.

Instead of using the skimmed lactic acid milk and curds, dried protein milk may be used (prepared by the Merrel Soule Co., Syracuse, N. Y., or Louis Hoos, Chicago). From 3 to 5 ounces of this dried protein milk is ground up with water and takes the place of the skimmed lactic milk and casein curds. This latter diet contains more fat, and this is a certain disadvantage; it is well tolerated, however, by most of the children.

During the periods of severe diarrhea cod-liver oil, spinach, orange juice, sugar, meat, eggs, and starch were omitted from the diet, and only one-half of the amount of curds added. The child was not forced to take more food than he desired. Prolonged starvation cannot be carried out with these infants, and food must be increased as rapidly as the digestive tolerance will allow. The digestive function varies from time to time and is very greatly influenced by conditions outside the gastro-intestinal tract, especially fever from any cause. Often, however, the food tolerance seems to vary when no cause whatsoever can be found. We have occasionally found it advantageous to add hydrochloric acid to the mixture before feedings. As much as 5 or 10 c.c. of normal hydrochloric acid, or a total of 1 ounce to $1\frac{1}{2}$ ounces is added to the entire day's feedings. We have seen good results from this procedure, but the acid addition cannot be kept up for more than two or three days at a time, as otherwise acidosis may develop.

This infant is now doing extremely well and his digestive function is much improved over what it was several months ago; he is now able to absorb a considerable amount of fat, less than 50 per cent. being eliminated in the stools; he has gained weight rapidly, and his stools, although still foul in odor and semiformed, are not more frequent than one or two a day. The child is not cured, however, and he will be almost certain to suffer subsequent relapses. The type of diet outlined will have to be kept up for years. Ultimately complete recovery may occur. It is probable, however, that for several years to come the child will be distinctly below normal in height, weight, and general development.

CLINIC OF DR. JOHN ZAHORSKY

ST. LOUIS CHILDREN'S HOSPITAL

THREE CASES OF ERYTHREDEMA (ACRODYNIA) IN INFANTS

A FEW years ago I encountered 3 cases of a peculiar affection, the symptoms of which did not coincide with any disease then known, and gave me no little concern, but which I finally classed as severe cases of pellagra. Dr. Bilderback, of Portland, and Dr. Patrick, of the same city, had seen similar cases, and the latter three years ago sent a description of one of his cases to Dr. J. L. Morse, of Boston, asking him to give his opinion as to the nature of the disease. Dr. Morse sent the description to Dr. Weston, of Raleigh, S. C., who concluded that the disease described was not pellagra, but after a study of the literature suggested that it may be the same affection described more than a half century ago by French writers and called "acrodynia." Dr. Weston read his paper before the Pediatric Section of the American Medical Association at the New Orleans meeting and considerable interest in this disease was aroused. Then appeared the critical study of 17 cases by Byfield and others, and the new syndrome received a definite place in our nosology.

The name of this disease is giving us considerable anxiety. I have also studied the literature, and in my opinion this disease is different from the classical acrodynia, a disease which occurred in adults only, that is, soldiers in camp or inmates of asylums, and may have been a nutritional disorder. The similarity of the clinical symptoms, however, is striking.

The name "erythredema" has been used by Wood and others, and seems to offer no great objection at least as a temporary name. I have the opportunity to show you 3 typical cases of this peculiar disease.

Case I.—M. V., boy, ten months old; the first-born in the family; was a healthy, active baby until the age of seven months, when a rash appeared on its body; since then he has not been thriving. He frets and lies on his face; he will not sit up or play with his toys. He is very restless at night and perspires continuously. He feels miserable and will not eat anything offered to him.

He has had no illness and has been breast fed entirely. The mother's diet is nutritious, consisting of milk, eggs, meat, potatoes, vegetables, and fruits. She does not eat much bread. The mother and father seem perfectly healthy young people.

Examination.—You notice a poorly nourished baby, weight 14 pounds, 6 ounces. The skin is dusky in color and the trunk is thickly covered with a fine papular rash. The skin and muscles are flabby and lack tonicity. He cries when he is handled as if movement produced pain or discomfort. The lymphatic nodes are small, but palpable in the neck, axilla, and groin. He closes his eyes when a strong light strikes them. The eyes are sunken, the fontanel depressed. He has 4 teeth and the mouth and throat appear slightly congested. The heart and lungs are normal; spleen not palpable, but the lower edge of the liver reaches $\frac{3}{4}$ inch below the costal margin.

Notice the peculiar hands and feet. The palms and soles are very red. This redness extends somewhat around the fingers and toes. Some desquamation is present in the palms. You observe his muscular weakness. He holds his head up with difficulty, cannot sit up, and seems unable to move his lower extremities. There is marked dermographia.

The superficial reflexes are absent everywhere, including the cremasteric and plantar reflexes. The deep reflexes are very weak or absent in the lower extremities, but present in the arms and forearms. No rigidity; no Kernig; no Chvostek.

The stool contained no pus-cells. The urine examination revealed nothing abnormal; no sugar, no albumin; no cells or casts.

The leukocyte count made several times in the course of a month varied only slightly—22,000. Differential count: Poly-

morphonuclears, 30; large mononuclears, 18; small mononuclears, 47; transitionals, 5. No eosinophils.

The von Pirquet test was negative. Wassermann test negative.

There has been little change in his condition during the month in which he has been under observation.

Case II.—M. L., girl, fifteen months old. This little girl has been sick two months. The first symptoms observed by the mother was restlessness and sleeplessness. She also noticed that her hands and feet were always cold. She refuses to walk, acts as though it hurts her to try to stand. She will not sit up, but can do so if coaxed. She frequently rubs her feet and almost continually scratches her genitals. She is constipated and has pain on urinating. She refuses to eat and prefers to lie quiet, but moans and frets. No fever has been observed.

This little girl was breast fed until ten months old, when she was placed on cow's milk and cereals. At the age of twelve months an eczema appeared on the face. The attending physician prescribed a diet of diluted cream, rye bread, and plenty of vegetables. The rash on the face disappeared, but there has been a marked tendency to the appearance of rashes on the body ever since.

There has been no previous illness, neither digestive nor respiratory, which the mother remembered.

Examination.—You will notice a moderately well-nourished child, with a slight papular rash on the body resembling prickly heat. The genitals are irritated from scratching. The hands and feet are swollen and the palms and soles red. They feel icy cold to the touch. No desquamation is present.

The gums look fairly healthy and the mouth shows 8 teeth. The cervical glands are palpable, but small. The heart, lungs, and abdomen seem normal. Rectal temperature 97.1° F. This patient has shown a subnormal temperature repeatedly. She objects to being handled in any way.

The superficial reflexes are very weak except the plantar, which also is much less active than it is found in health. The

patellar reflex cannot be elicited. The Achilles reflex is negative. The ulnar reflex is rather exaggerated. The leukocyte count was 21,000. Differential count: Polymorphs., 60; large mononuclears, 10; small lymphocytes, 32. Von Pirquet negative. No Wassermann was made.

Case III.—J. N., boy, eighteen months old. The only child of young healthy parents, was breast fed until thirteen months old. He seemed well and strong until six weeks ago, when he had a slight digestive disturbance with moderate diarrhea, was cross, and irritable. Received a lot of purgative medicine. No fever was noticed. An ulcer was observed in his mouth at the onset of the disease. He feels miserable, has no appetite, and refuses to walk and play. He has had no respiratory disease of any kind. He lies in his go-cart and sucks his thumb nearly all the time. He often gags himself with his hand.

Examination.—Skin slightly dusky, but no eruption. The gums are red and swollen, especially around the left upper canine and the lower central incisors. The left lower central incisors are loose in their sockets and one appears ready to fall out. The eyes are sunken and the body is poorly nourished. The muscles are flabby and lack the proper turgescence. The hands and feet are red, the fingers markedly swollen and desquamating. On the right thumb is found an ulcer covered with necrotic epidermis.

The internal organs show nothing wrong. The abdomen is distended and tympanitic. He seems sore on handling and refuses to sit up or stand.

The superficial reflexes including the plantar are absent. The patellar reflex was markedly exaggerated two weeks ago, but now it is very feeble.

The leukocyte count was 14,600 at the first visit two weeks ago, now the count is 20,500. Rectal temperature 98.2° F. A few pus-cells (pus index 15) found in the stools. Urine negative.

Let me summarize the common symptoms in this syndrome: The gradual, insidious onset, the peculiar tendency to an erythematous or morbilliform eruption, the paresthesia of the

skin, the muscular weakness, the change in disposition, the anorexia, and the swollen red hands and feet. In severe and protracted cases a striking alteration occurs in the nervous system. At first an exaggeration of the deep and superficial reflexes is apparent. Later these reflexes become obtunded, diminished, and finally suppressed. The muscular weakness may become so great that the young child is helplessly paralyzed.

The eruption is not characteristic. Most cases resemble aggravated cases of prickly heat. Sometimes the rash may be mistaken for scarlet fever by its punctiform appearance. A morbilliform eruption has been observed. Patches of erythema are not uncommon. The rash generally covers the trunk, but may be found on the face and extremities. Sometimes small spots of erythema occur only on the hips or thighs. Desquamation of the erythematous patches may repeatedly be observed. A very characteristic symptom is the swollen hands and feet. The palms and soles have a livid, swollen appearance. The fingers are red and thickened and often scales of epidermis are discovered still clinging to the skin between them. The dorsal surface of the hand also is usually red and swollen. The feet have a similar appearance.

A marked change in the sensation of the skin is evident, hyperesthesia is most common. One of my cases showed large areas of anesthesia on the thighs and abdomen. Nearly all scratch their skin, especially the lower abdomen and genitals. Many like to have their feet rubbed. Still the movements of their limbs, as a whole, produces pain or discomfort and they prefer to lie inactive.

A most alarming symptom to the parent is the great change in the disposition. The child was happy, active, and playful, now is inactive, whimsical, irritable, never satisfied, and does not sleep. In fact, it wakes up dozens of times at night and cries. The lack of appetite is often so marked that forced feeding has to be resorted to.

Still greater significance must be attached to the morbid changes occasionally found in the gums, when the hard alveolar process becomes soft, the teeth loose in their sockets, and actually

drop out one after the other, a phenomenon almost unknown in any other disease except poisoning from mercury or phosphorus.

With all these toxic symptoms there is no fever, even a subnormal temperature is common.

The most remarkable change of all is the presence of a high degree of leukocytosis, mostly an increase in the lymphocytes, but the polymorphonuclear cells also are augmented in numbers, which places this disease in a category of its own.

I have seen and watched the course of 15 or 16 cases of this peculiar disease, and have been perplexed by the peculiar recrudescences in the symptoms. The symptoms vary at different times and are entirely uninfluenced by our therapeutic efforts. Like so many diseases there seems to be a definite time limit, although its duration varies considerably from a few weeks to many months. The child nearly always gets well, no matter how distressing and serious the condition seems at times, and how discouraging the task appears to the parent and physician. The prognosis is almost invariably favorable, and the wasted, helpless infant becomes a strong healthy child.

Certain complications are often encountered. Digestive disturbances may arise from incautious efforts at overfeeding, but, as a rule, the child is constipated. A more common and serious complication is the distressing tendency to respiratory infections, bronchitis, and especially pneumonia; 4 of my cases passed through an attack of lobar pneumonia. One patient suffered twice in the course of three months from this serious disease, yet it is doubtful that these respiratory infections have anything to do with the causation of the disease. It is gratifying, however, that these miserable creatures really show a remarkable good resistance toward these respiratory infections. The course of the pneumonia is fully as short and favorable in them as in the average healthy baby. I have had the strange experience in 3 cases of seeing a rapid amelioration of a prolonged and severe erythredema after an attack of croupous pneumonia, as if this disease in some way removed the poison which caused the primary affection.

What is the nature of this disease? On account of its sin-

gular manifestations not even a working hypophysis has been offered that will stand the test of clinical criticism. Because the disease resembles somewhat pellagra and also beriberi, it was suggested that it must be a deficiency disease. It is in vain, however, that we have searched in the dietetic history of the child for some clew as to the food substance that might be inadequate for proper nutrition. So many of these patients are infants naturally fed. We have inquired carefully into the nutritive condition and the dietetic habits of the mother, and found nothing different from other mothers who have perfectly healthy children. Even in the case of infants weaned for a prolonged period no gross dietetic disorder could be found. True, some of them never had good appetites, but this weakness is so common in young children, and while it may retard growth, does not provoke the syndrome under discussion.

Another objection to the theory of a deficiency disease is found in its peculiar protracted form. Having supplied an abundant dietary with plenty of mixed proteins, with an excess of fat-soluble and water-soluble vitamins, one should expect a reasonable effect of this effort. But in spite of our care the disease continues with its stages of amelioration and recrudescence for an indefinite time, and then suddenly an acute disease, like pneumonia or enteritis, changes the clinical features, or convalescence begins rather abruptly without definable cause.

A third objection to the theory that this is a deficiency disease is found in the presence of a leukocytosis. A leukopenia is what we should expect from the study of known deficiency diseases.

Another suggestion has been offered, namely, that the disease is a polyneuritis following influenza. It is hardly necessary to dwell on this. Only in 2 of my cases could any such connection even remotely be established. These children are subject to respiratory infections, but the disease does not commence with grippal symptoms, and I have seen not a single such case develop in the pandemic of 1918–19 in the observation of several hundred cases of true influenza.

For a time I was rather inclined to view the hypothesis of

mineral poisoning with favor. Several of my patients had been given large doses of calomel at the onset of the disease, and the swollen gums, loosened teeth, with salivation, gave support to this. However, cases were encountered in which no history of calomel administration could be elicited, and this drug as a possible cause was dismissed.

It appears that some powerful protein poison must be present, whether it attacks the nerve terminations primarily and the other symptoms are secondary is possible, but it is hard to conceive of the loosened tooth as a trophoneurosis. The marked change in the disposition of the child suggests some cerebral alterations. The complete paralysis with absence of the deep reflexes points to a disease of the cord. As far as I know no postmortem study has as yet been made on an uncomplicated case of erythredema.

The diagnosis offers no great difficulty when you have seen one or more typical cases. At the onset some doubt may arise, especially in the presence of an intense erythematous rash. The afebrile young child who has been active, but now feels miserable and lies quiet and whines all the time, should suggest the possible presence of this disease. If there is clear evidence of a paresthesia of the skin with recurrent rashes, and especially if the hands and feet are cold to the touch, but appear livid and swollen, the diagnosis is almost certain. When we examine the state of the gums and teeth, study the voluntary movements of the child and also the reflexes, we get additional evidences. The leukocyte count is very important, as I know of no afebrile disease with such a large number of leukocytes in the blood, except, of course, the leukemias.

Since we have only unsupported hypotheses to explain the origin of this peculiar disease, the therapy must be entirely empiric. The poor nutritive condition suggests forcible feeding of a diet containing an abundance of protein and fat and also relatively rich in vitamins. Our therapeutic effort should be directed principally toward the maintenance of a perfect nutrition. This meets with extreme difficulty in these cases on account of the severe and protracted anorexia. A definite quantity

of food must be prescribed and the attendant directed to administer this with patience and persistence. Occasionally tube feeding may have to be used.

All of my little patients suffering from this disease have received cod-liver oil, malt extract, and small quantities of iodin. I am not sure that it has any great value.

We have tried for short periods a great variety of empiric remedies. Thyroid extract, pituitary extract, and mixed glandular extracts appeared to have no influence on the course of the disease. In 2 cases mercury was given, but the symptoms became aggravated. Phosphorus, iron, and arsenic gave no recognizable results. The injection of a foreign protein in the form of a mixed vaccine suggested a detrimental influence.

It seemed worth while to try the commercial vitamins, the physiologic effect of which is in dispute. Tablets and powders of mixed vitamins were given in several cases, but not the slightest benefit could be detected.

The iodids were given in average doses in 4 cases, and this is the only drug which suggested to us some therapeutic value. This, however, was merely a clinical impression and may not mean anything.

We have tried the effects of sunlight by placing the children exposed to the sun for an hour or more during the day, without effect. Hot weather aggravates the skin lesions and has a tendency to derange digestion.

Symptomatic treatment must not be overlooked. The protracted insomnia sometimes is benefited by the administration of a narcotic or soporific. Bromids do no good and aggravate the skin lesions. The distressing itching of the skin calls for some soothing applications. Ulcers and boils of the skin must be treated. Antiseptic applications to ulcers of the mouth must sometimes be used.

In short, feed and take care of the little patients, and they will ultimately get well if no serious complication arises.

CLINIC OF DR. J. CURTIS LYTER

ST. ANTHONY'S HOSPITAL

BRONCHOPULMONARY LITHIASIS

I HAVE for our first clinic this morning 2 rather interesting cases presenting a very infrequently encountered symptom-complex. A symptom-complex probably best designated "active bronchopulmonary lithiasis."

Probably before attempting to study the cases it will be very desirable indeed for me to review with you some of the former conceptions of this symptom-complex, especially as they relate to the French clinicians, some of our own conceptions, and attempt to delineate in a way some of the problems for the future studies of this very intricate, but interesting problem.

Bronchopulmonary lithiasis, if by the term one intends to describe the passage of a calculus, osseous, cartilaginous, or calcareous, from the lower respiratory tissues through the bronchi and trachea to the exterior, is in no event a frequent symptom-complex. Its infrequency associated with the ease by which the only pathognomonic sign, the expectoration of the calculus, escapes detection probably in the best way explains the sparse literature on the subject. However that may be, Paulalion in 1891 presented a thesis to the Academy of Medicine at Paris, in which he considered the subject at great length.

Paulalion presented the subject of "Les Pierres du poumon, de a plevre et des bronches" so minutely and so clearly as to render it most difficult for clinicians to amplify or extend his observations until stereoroentgenography of the thorax became accepted as a great diagnostic adjunct. With the perfection of thoracic stereoroentgenography one is able to study the size, shape, and location of the calculi while simultaneously studying the associated pathology, which is the etiologic basis upon which

the lithiasis develops. The symptom-complex to be here considered is the result of the formation and expulsion of concretions which may be cartilaginous, osseous, or calcareous, depending certainly upon whether the preceding disease attacked the cartilaginous, osseous, or soft tissues of the bronchopulmonary system.

The cartilaginous concretions, "Les productions cartilaginoforms," of Paulalion's description, arise most probably from the bronchial cartilages as a result of destructive processes associated with simple inflammatory, malignant, syphilitic, or tuberculous invasions. Arising from the destructive invasion of the bronchial walls are true chondral sequestræ, which during their passage toward the exterior produce the symptom-complex of active bronchopulmonary lithiasis. Paulalion in his masterful description depicts the symptom-complex as the result of the passage of a mass of dense fibrous tissue simulating very closely cartilaginous tissue.

The production of osseous concretions is associated with chronic bronchopulmonary tuberculosis, fibrinous pleurisy, and pulmonary abscess formation. While some of these concretions have been demonstrated to contain osteoplasts and haversian canals, thereby presenting irrefutable evidence of their histologic nature, their exact origin remains quite in question. As described by Paulalion and his venerated teacher, Dieulafoy, the osseous concretions present themselves as nodular, diffuse, or irregularly ramifying masses. They describe their origin to bronchial dilatation, chronic bronchopulmonary tuberculosis, and chronic fibrous pleurisy. Although there is no direct evidence bearing upon the question, it is more than probable that these concretions result from ossification and new bone formation in the tracheal and bronchial cartilages which have been invaded by some chronic infection. It is altogether possible in destructive diseases involving the chest wall and lungs for a sequestrum of bone from the sternum, ribs, or vertebræ to find its way into the air-passages, and produce the complex of symptoms.

Properly speaking, the true syndrome of bronchopulmonary lithiasis results when a calcareous mass, formed in the bronchial

or pulmonary tissues, is extruded into a bronchus and passes toward the exterior. Calcareous concretions are formed by the calcification of bronchopulmonary tissue or lymph-glands. The most frequent and probably the only cause of such calcifications is chronic tuberculous infection in individuals, who manifest marked tendencies toward healing by cicatrization and calcification. There are probably at least two conditions necessary for the production of calcareous concretions in the course of chronic glandular, bronchial, or pulmonary tuberculosis, the first condition being the necrosis of the infected tissue, while in the second place must occur the deposition of calcium salts, usually the tribasic phosphate or the carbonate.

There remains as unsolved an interesting problem in relation to the healing of glandular, bronchial, and pulmonary tuberculosis by extensive cicatrization and calcification. The two processes are not necessarily inseparable, as the one is frequently observed in the absence of the other. Especially is this true of extensive cicatrization. Extensive glandular, bronchial, and pulmonary calcification may eventually be observed to occur only in those individuals who exhibit certain types of constitutions, and in whom the mineral metabolism varies from what is considered a normal course by physiologists. This problem lies well within the realm of clinical observation, and when once definitely solved will markedly enhance the knowledge of prognosis in tuberculous infections in certain types of individuals. This field of thought has remained hitherto confused and almost entirely unexplored.

A similar course of logic can probably be followed in other pulmonary conditions which are more rare than tuberculosis, namely, infarct or abscess formation. Similar to tuberculosis, these pathologic conditions not infrequently have marked calcification as an associated phenomenon.

It is scarcely probable that extensive cicatrization and calcification are enhanced by some peculiar chemical or biologic character or the organism invading the lung tissue, since the two phenomena are observed under such widely varying pathologic processes.

Extensive calcification once ensuing, the individual becomes, at least potentially, a case of bronchopulmonary lithiasis. Whether the active syndrome associated with the passage of a concretion from the glandular, bronchial, or pulmonary tissues into and through the bronchi, trachea, and larynx develops or not depends upon some very important conditions, the first of these conditions being the accessibility of the bronchial passages to the concretion. Since the concretions are most frequently encapsulated by fibrous tissue of varying thickness and density, it necessarily follows that this fibrous capsule must be broken either by increased internal pressure or active pathologic changes tending toward destruction of the capsule before the concretions can enter the air-passages.

Other important conditions, such as the size of the concretion in relation to the transverse diameter of the adjacent bronchus and its anatomic relationship to the bronchi, will very frequently determine whether they are to remain latent and symptomless or migratory, under which circumstance the active symptom-complex to be delineated below may ensue.

When the concretion in its transverse diameter is much larger than the adjacent bronchus its passage toward the exterior is quite improbable, even though the enclosing fibrous capsule be ruptured. Under this circumstance the formation of a new capsule is probably the rule. Migration is likewise rendered impossible when the concretion is far removed in its anatomic relationship from a bronchus of adequate size. That one or the other of these conditions exists in a vast majority of instances of bronchopulmonary calcification is, indeed, most fortunate, as under these conditions the concretions are latent and the patient remains unmolested.

Symptomatology.—In the greater number of cases the concretions remain always latent and symptomless because of the continued intactness of the enclosing capsule or of the relative smallness of the adjacent bronchus. Finally, latency is the only physical possibility in those cases where the concretion, in its anatomic relationship, is far removed from any bronchus.

The existence of one or more of these conditions renders the

great majority of the calcareous concretions latent and symptomless, irrespective of whether they originate in the glandular, bronchial, or pulmonary tissues.

When the concretions become migratory, enter a bronchus, and are being expelled, symptoms of greater or less severity arise and persist until the expulsion of the concretion is accomplished, or until it redescends into the lower air-passages to produce later a syndrome more or less characteristic.

The symptoms associated with the migration and expulsion of a concretion may be very mild and composed of a slight paroxysmal cough, with slight or moderate thoracic constriction. During the paroxysm of coughing the concretion may be expelled into the mouth and recognized by the patient, or it may be expectorated with a mass of sputum, and remain unrecognized by either patient or physician. From this very slight manifestation the symptoms may vary to an intensity quite alarming alike to the patient and physician. In the more severe syndromes the onset is sudden, with pronounced thoracic oppression, poststernal pain, grave distress, a sensation of constriction, slight or distressing dyspnea, and, as Paulalion has so aptly expressed it, "a sensation of anguish or tearing either in the poststernal region or at the sides of the chest." Immediately subsequent to the onset of these symptoms a paroxysmal cough appears, and continues until the concretion is either expectorated or redescends into the lower air-passages, when immediately the entire syndrome abates, and the patient is again comfortable.

The more severe attacks have been compared by Dieulafoy to attacks of biliary or urinary colic. Paulalion gave to them the very descriptive name of "Colique bronchique et pulmonaire." Associated with or immediately following the expectoration of the concretion there is very frequently some hemoptysis. Usually this is small in amount and only rarely profuse. At times it may precede the expulsion of the concretion by several days.

In those instances where the concretion is expectorated immediate recovery, even though it be temporary, ensues. When the concretion redescends into the deeper air-passages it be-

comes an ordinary foreign body, producing the clinical course commonly observed when a foreign body gains access to the lower respiratory tissues. It is then that fever, which is, as a general rule, absent, is present and irregular. A persistent and usually productive cough supervenes; while anorexia, loss of weight, and other symptoms indicative of pulmonary infection are constantly present.

Physical exploration of the chest which until this time revealed evidence only of chronic disease or no evidence at all, may now uncover the physical signs, usually associated with pulmonary infection and infiltration. While in this condition the patient is considered to be the subject of active and progressive tuberculosis, and little thought is given to the real cause of the acute pulmonary syndrome. Perhaps it was this syndrome, observed by Dieulafoy, which caused him to write a paragraph which I shall translate almost verbatim: "In other circumstances the chronic evolution of the lithiasis simulates tuberculosis when there does not exist at all the tuberculosis. It is pseudopulmonary tuberculosis of calcareous origin (Paulalion). In the course of time the patient is taken with a cough, at first dry, and then accompanied by a mucopurulent sputum. The symptoms increase, and one frequently establishes the signs of induration, pulmonary congestion, localized bronchitis, and likewise the signs of small cavities. The general state becomes bad, with emaciation and night-sweats. Hemoptysis is not rare, but the attention is, above all, attracted by the dyspnea and pain; the one and the other returns by fits and starts of more or less intensity, until the time when during a crisis of coughing, more violent than any other, the patient renders a calculus with or without hemoptysis. Thence all of the symptoms are ameliorated in a definite fashion when there is only one calculus, and for a time only when there are many calculi; the expulsion of which will always be preceded by a period of aggravation of symptoms. Never in this form does one find the Koch bacillus in the sputum."

Certainly in that paragraph Dieulafoy describes a condition produced by a calculus, which, incompletely expelled, rede-

scends into the deeper tissues, producing infection and infiltration or a condition resulting from a secondary infection around a calculus situated in the pulmonary tissue proper.

One is able to observe in most of these patients a state of general nutritional inferiority, vasomotor instability, neurotic symptoms of a mild and unclassified type, coarse and dry skin, dry and thin hair, capricious appetite, and slight or moderate debility.

So pronounced are certain physical features of patients who show marked glandular, bronchial, or pulmonary calcification that one is inclined to ponder over the possibility of some abnormal metabolic state as a factor in marked calcification as a part of the healing process of infections in these tissues.

In his classical description of bronchopulmonary lithiasis Dieulafoy has detailed many complications, among which acute bronchitis, pleuropneumonia, pulmonary abscess, pyopneumothorax, and sudden death from obstruction of a large bronchus are the most important.

In the two personal observations here delineated only one complication was recognizable, that being pulmonary consolidation followed by pleural effusion.

Case I.—The first case, gentlemen, is a married lady thirty-six years of age, who enters our medical service with the following history: About six years ago there developed suddenly a paroxysmal cough, dyspnea, moderate thoracic constriction, and some poststernal pain. After coughing for about fifteen minutes the patient expectorated a small, cubical stone. Immediately the cough, dyspnea, and pain subsided, and complete comfort ensued. During the six years the patient has been able to collect some 40 stones expectorated during paroxysms more or less severe. Upon two occasions a small hemoptysis accompanied the expectoration of the stone.

Physical examination, upon entrance, reveals a thin, poorly nourished lady with atonic skeletal muscles, long and thin bones, coarse and dry skin, thin and dry hair, pale mucous membranes, and rather marked debility. Exploration of the

chest reveals moderate bilateral emphysema and moist râles, with increased inspiratory murmur over the right scapulovertebral space. The remainder of a complete physical and clinical study makes no revelations of importance.

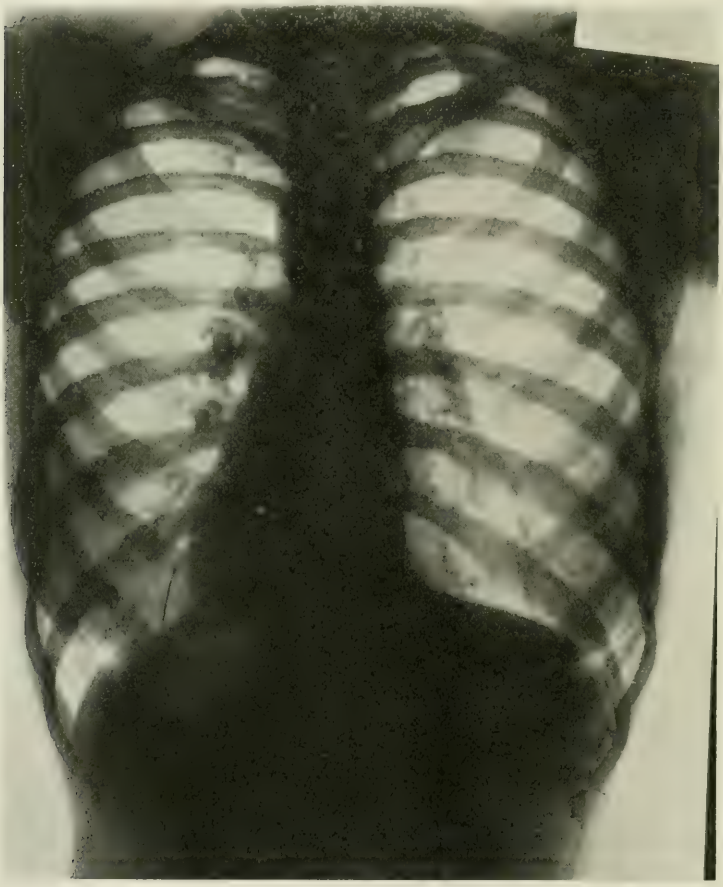

Fig. 44.—Case I, revealing calcareous mass in left hilus. This patient expectorated over 40 calculi.

The stereoroentgenograms of the chest are striking, as you see. The lungs are singularly clear. The heart and large vessels apparently normal. Located slightly above the right hilus

shadow can be observed a mass of calculi, probably calcified lymph-glands. This mass can be seen to be composed of numerous small calculi. By an ulcerative process this mass periodically discharges calculi into the adjacent bronchus. One year has elapsed since the initial observation of this patient, during which period she has expectorated 6 calculi; the expectoration being usually preceded by a cough, thoracic oppression, poststernal pain, of greater or less severity, and dyspnea.

Case II. – The second case is that of a young lady nineteen years old, initially observed on the medical service of St. Anthony's Hospital during the month of December, 1920. She presented to us a history of temperature of a moderate degree for six months, irregular, evanescent, and exacerbated by either physical or mental exercise. There was during this time a paroxysmal cough accompanied by severe thoracic oppression and a poststernal pain. This syndrome was frequently followed by the expectoration of a bloody mass of sputum, which the patient or her physician had not at any time carefully examined.

By a physical search of the chest at this time one was able to elicit an accentuation of the inspiratory murmur, a prolongation of the expiratory murmur, increased whispered voice sounds, and a moderate number of subcrepitant râles over the left scapulovertebral space.

Stereoroentgenograms made at this time reveal, as you see, a large number of calcareous masses lying in the left hilus shadow and scattered throughout the left lung. To a less extent the same condition prevails through the right hilus shadow and lung. A diagnosis of glandular and pulmonary tuberculosis with extensive calcification was made.

In April, 1921, while remaining under personal observation, the young lady suddenly developed a temperature of 102.4° F., pulse 110, respiration 34, cough, profuse expectoration, dyspnea, and a stabbing, inspiratory pain in the left axilla. Exploration of the chest rendered the findings of pulmonary consolidation over an area about 3 inches in diameter in the left axilla. Since

the leukocyte picture was that of a rather pronounced polymorphonuclear leukocytosis, a diagnosis of acute pneumonia was made, although the sputum examination for the purpose of typing the organism failed to reveal any virulent pneumococcus.

Fig. 45.—Case II, presenting large numbers of calcareous areas throughout each hilus shadow and lung. This patient has expectorated 2 stones.

The cough continued more or less paroxysmal, and on the sixteenth day of the acute illness the patient, after a severe attack of coughing, thoracic oppression, and poststernal pain, expectorated a quantity of bloody sputum in which was found

a calcareous concretion about the size of a small pea. Improvement immediately ensued, and the former state of health soon prevailed.

About two months later during an attack of coughing a second concretion was expectorated, following which there was a slight pulmonary hemorrhage. The accident occurring at the time of the pulmonary consolidation is at present easy of analysis. A concretion was expelled from its usual position, and partially ascended the air-passages, only to redescend into the deeper air-passages during a deep inspiration, where it became a foreign body, producing the localized tissue changes familiar to all. When the concretion was again dislodged and expectorated, recovery of the pneumonia was prompt.

These 2 cases conform very well indeed to what may be designated active bronchopulmonary lithiasis. Every clinician, with the opportunity for close study of thoracic diseases, especially with the aid of stereoroentgenograms, soon realizes the frequency of marked pulmonary and glandular calcification, every case of which should be considered as potentially a case of bronchopulmonary lithiasis. Whether or not these potential cases become active will depend upon the condition described above.

By keeping such possibilities constantly in mind one will be able to recognize the active stage easily, and to discover in this the true etiology of some pulmonary syndromes, which are at times associated with the expulsion of a concretion.

In concluding may I not express the opinion that in the cure of pulmonary and glandular tuberculosis by calcification one may recognize a process of peculiar metabolism, probably associated with physiologic features of lymphoid and pulmonary tissues which are at the present time unsuspected.

MEDIASTINAL TUMOR WITH THE RESULTS OF *x*-RAY TREATMENT

THE second clinic, gentlemen, is that of a tumor occupying the superior portion of the mediastinum. The patient is a gentleman fifty-four years of age who first came to my service here on February 4, 1921. At that time he gave the following history: Immediately following an attack of influenza in February, 1920 he developed a rather severe pain in the upper portion of the right chest anteriorly, radiating to the shoulder and into the right arm. This pain was described as having a rather marked exacerbation during exercise and was to some extent relieved by rest. Associated with the pain was a harassing and unproductive cough. The cough, like the pain, became much worse upon exercise and was relieved by rest. The other symptoms presented at this time were night-sweats, tinnitus, exertion dyspnea, tachycardia upon exertion, edema of the face and neck noticed only upon arising, disappearing through the day, and anorexia. There has been a loss of about 20 pounds in weight during the previous six months.

Physical examination at this time revealed some edema and cyanosis of the face, head, neck, and shoulders. There was a moderate bilateral exophthalmos. The superficial veins of the anterior portion of the chest and of the shoulders were moderately distended.

The chest examination was almost classic in its revelations. There was a very positive D'Espine's sign as low as the sixth thoracic vertebra. The poststernal dulness at the first and second interspaces was 9 cm. in its transverse diameter. The suprasternal notch was bulging as though from substernal pressure. A slight systolic friction-rub was audible at the apex of the heart. The aortic and pulmonic second sounds were scarcely audible. Otherwise there were no abnormal physical findings noted upon a carefully conducted physical examination

of the entire body. A careful investigation of the urine and blood, including a Wassermann reaction, was likewise negative.

An *x*-ray plate of the chest, as you note in Fig. 46, presented a beautiful shadow, apparently due to a tumor lying posterior to

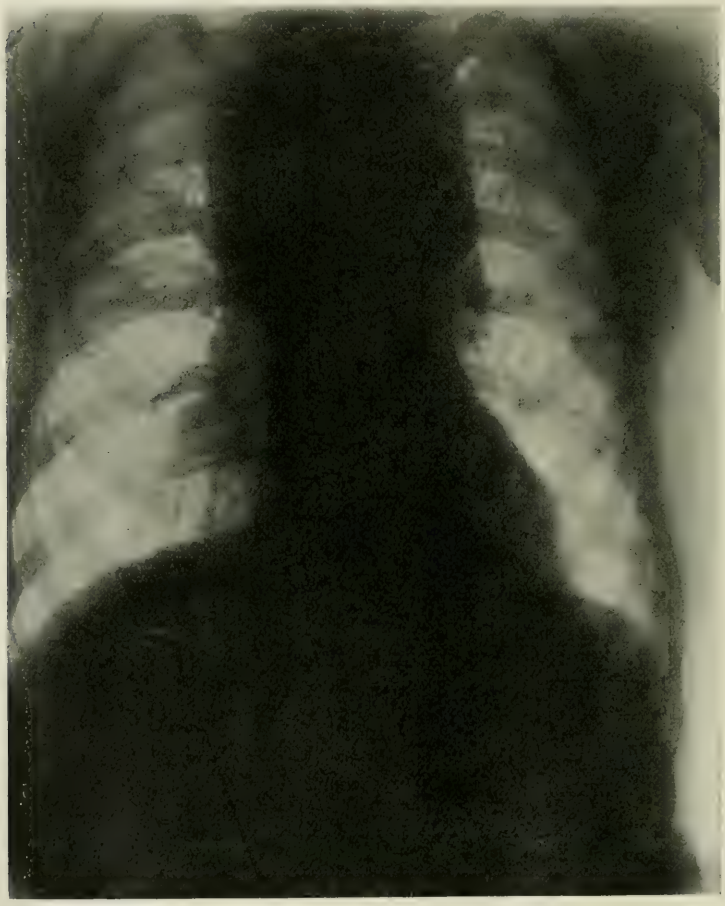

Fig. 46.—Revealing large shadow in the area of the thymus gland. Plate taken for diagnostic purposes.

the manubrium and occupying the anatomic site of the thymus gland. The shape of the tumor conforms very well indeed to that of the thymus. The tentative diagnoses at this time were:

(1) Malignancy of the thymus.
(2) Lymphosarcoma of superior mediastinum.
(3) Mediastinal Hodgkin's disease.

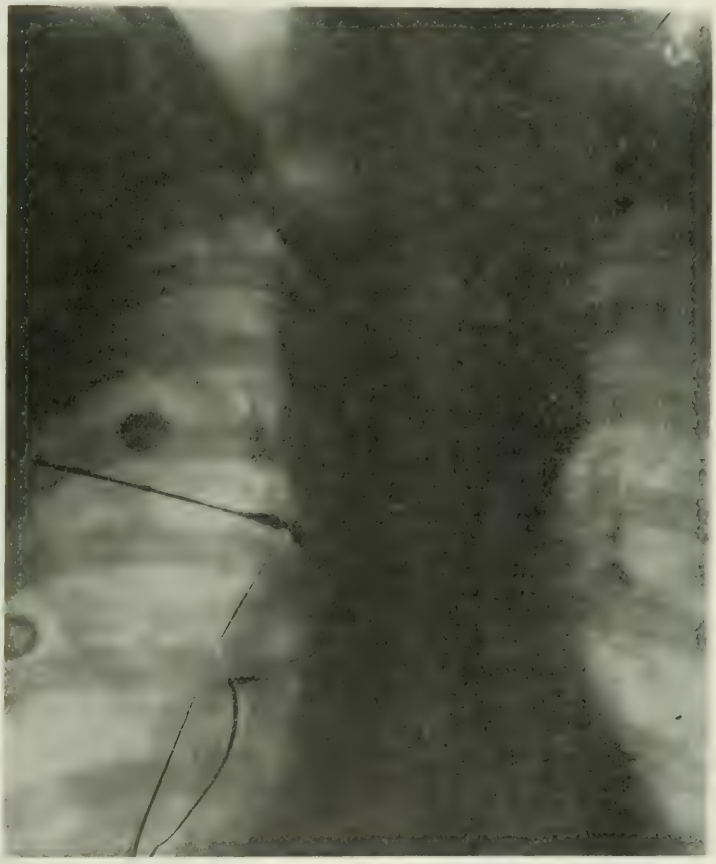

Fig. 47.—Revealing the same tumor mass as Fig. 46 after about fifteen Roentgen treatments.

The patient was referred to the Roentgen department of the hospital for deep Roentgen therapy. I will now present to you the *x*-ray plates, which in the most spectacular manner demonstrate the results obtained by our roentgenologist. Figure 46, as you know, was taken for diagnostic purposes. Figure 47

was taken after fifteen *x*-ray treatments. Figure 48 after thirty treatments, and Fig. 49 after forty treatments. The time consumed in giving the forty treatments was approximately eight months.

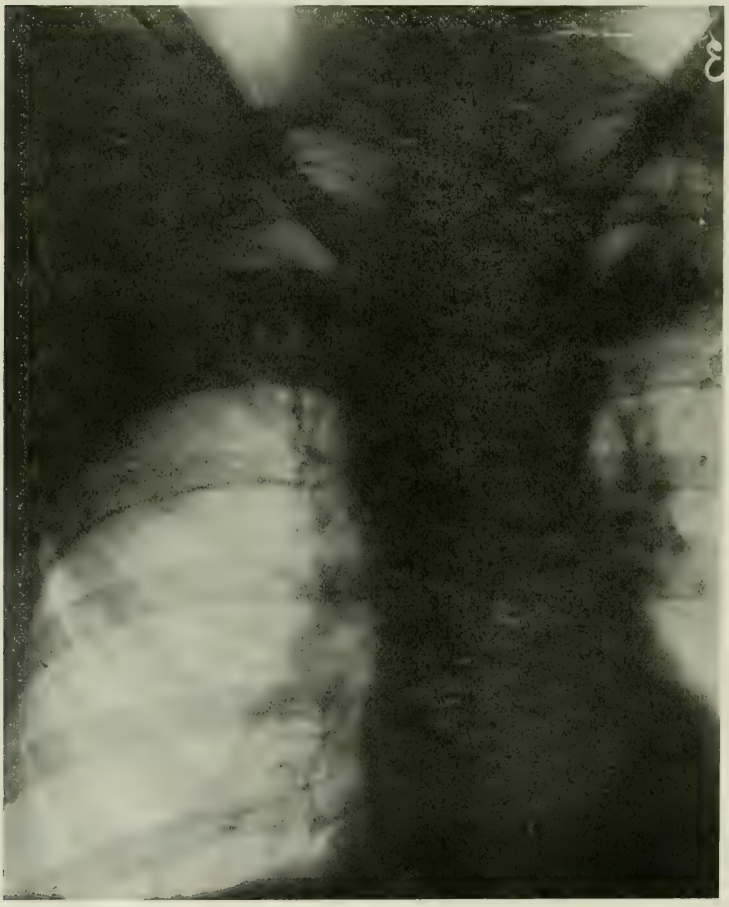

Fig. 48.—Revealing the same tumor after about thirty Roentgen treatments.

At the beginning the treatments were given every third day, while later a period of one month intervened between the treatments. We can see from this series of plates that the tumor

gradually disappeared until it was hardly discernible in the *x*-ray plate.

Fig. 49.—Revealing the same tumor after about forty Roentgen treatments. The plate is taken at a slight angle; consequently reveals the arch of the aorta more distinctly.

Almost from the beginning of the treatment the patient was relieved of his pain and cough, the appetite improved, he gained about 15 pounds in weight, and considered himself practically well. At this time he disappeared from our observation for a

period of about two months, when he returned, complaining of a recurrence of the pain, a productive cough, loss of weight, and dyspnea.

At this time an *x*-ray plate (Fig. 51) was made at an angle of 45 degrees so as to reveal the contents of the posterior mediastinum, and, as you can see, reveals a shadow, probably a tumor, lying posterior to the heart and large vessels and practi-

Fig. 50.—Revealing the large distended epigastric veins.

cally filling this portion of the mediastinum. At this time he was given more *x*-ray therapy, and again permitted to leave the service.

He returned to the service again only a few days ago, and presented the picture which I am able to show you now. You will note a rather marked degree of general emaciation, an emphysematous type of chest, dry, scaly, coarse skin, evident

respiratory distress, almost continuous cough, with a production of a large amount of thick, yellow sputum. The veins on the abdomen are greatly distended, and those over the chest, espe-

Fig. 51.—Plate made at angle of 45 degrees revealing tumor between the large vessels and the spine in the upper portion of the mediastinum.

cially on the right side, moderately distended. In tracing the course of the blood through the superficial veins we find that the blood in the internal mammary veins is passing down through

the superficial epigastric veins to reach the inferior vena cava. These veins have gradually enlarged until at the present time they are probably of the same diameter as a lead pencil. It can

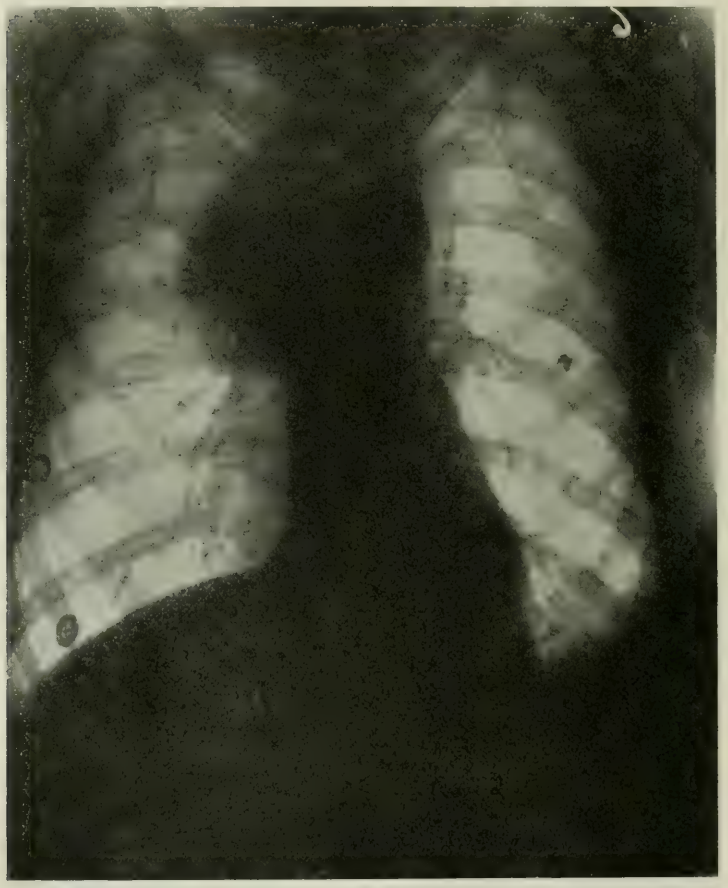

Fig. 52.—This plate, taken March, 1922, reveals the tumor growing well into the upper lobe of the right lung.

be noted also that the veins on the left side of the chest and abdomen are slightly distended.

Upon physical examination at the present time we find an area of dulness extending to the right of the sternum for a

distance of about 9 cm., this area of dulness occupying the first, second, and third interspaces. D'Espine's sign remains positive. The trachea is apparently displaced to the left, causing an in-

Fig. 53.—Taken April 21, 1922, revealing a growth of the tumor over the previous plate. In this plate the tumor apparently is growing to the left as well as the right.

crease in the tactile fremitus and the spoken and whispered voice sounds to the left of the first four thoracic vertebræ. There are not at the present time, and have not been in the past, any auscultatory signs which might in anyway indicate the presence

of an aortic aneurysm. Likewise, in viewing the tumor under the fluoroscope, no pulsations are observed. An *x*-ray plate made a few days ago reveals, as you note in Fig. 52, the tumor mass extending well into the area of the upper lobe of the right lung.

It has been very beautiful indeed to observe the course of this tumor in its progress, interrupted as it was for a while by energetic Roentgen therapy, and probably having its natural course changed to some extent by this same therapy, but finally revealing all of the classical physical phenomena of mediastinal pressure.

The great distention of the right internal mammary and superficial epigastric veins with the course of the blood being downward certainly can only be interpreted as the result of an obstruction of the right innominate vein by the tumor. Likewise the very moderate distention of the left internal mammary and epigastric veins indicate a partial obstruction of the left innominate veins. This is verified in Fig. 53, revealing as it does a slight shadow to the left of the sternum. The clinical and Roentgen evidence in this case is that of a tumor occupying the superior mediastinum with metastasis into the mediastinal lymph-glands. With the exception of the inhibition upon the growth of this tumor by energetic Roentgen therapy the course of the tumor has been gradually progressive, and as the tumor has progressed the general condition of the patient has failed until I have seen him changed from a fairly robust, well-nourished, comfortable, and active gentleman into an emaciated, frail, weakened patient; revealing, as I said before, dry, scaly skin, wasting of the muscles, and the disappearance of the adipose tissue. We have been able, likewise, to observe the gradual development of the collateral venous circulation, enabling the blood from the upper extremities to gain access to the inferior vena cava.

A great deal can be said relative to the differential diagnosis of mediastinal tumors. Tumors in this location are very similar to those in the nervous system. The diagnosis of the tumor itself and its localization is not a matter of great difficulty, but to state the precise nature of the tumor is in a great many cases

absolutely impossible. Ideas we have certainly, but we all recognize that our ideas relative to the type of tumor present should be elastic ones always.

I believe, since there is no anatomic evidence of syphilis elsewhere in this patient, and since the Wassermann reaction is negative, we can exclude syphilis. I believe, too, that large masses of tuberculous lymph-glands can be excluded because of the absence of tuberculosis in the lung tissue, the absence of fever, and for many months a normal pulse-rate. I have observed mediastinal Hodgkin's disease in association with peripheral Hodgkin's disease. I have never seen the lymph-glands in Hodgkin's disease enlarged in this portion of the mediastinum, probably due to the fact that there are very few lymph-glands this high up in the mediastinum. Likewise, I have seen 2 cases of Hodgkin's disease with mediastinal tumors thoroughly *x*-rayed, with no diminution in the size of the tumor. This experience together with the absence of any palpable lymph-glands in the axilla or cervical regions in this patient leads me to doubt very seriously the diagnosis of mediastinal Hodgkin's disease in this case. I think aneurysm was definitely excluded in our former discussion. We occasionally see a cyst of some type occupying a position in the mediastinum, and, as Hertzler has taught us, these cysts have a tendency to work upward and eventually appear in the suprasternal notch, from which site he has removed several. The configuration of this tumor could hardly be that of a cyst. Likewise, the position of it would be very unusual for a cyst. Its growth and rapid response to *x*-ray treatment are strong points against a diagnosis of a cyst. Probably the best diagnosis lies between a lymphosarcoma and a malignancy of the thymus gland. The first is more common, but is usually found around one or the other hilus where the lymph-glands are more numerous. We are not capable, however, at the present time to exclude lymphosarcoma or malignancy of the mediastinum, and I think for the present our diagnosis must remain, in so far as the type of tumor is concerned, between these two. The patient will be observed, and if an autopsy is possible at all, the autopsy findings will be reported later.

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THE RELATIONSHIP OF SYPHILIS TO THE APPEARANCE OF SYMPTOMS OF DISORDER OF THE CENTRAL NERVOUS SYSTEM

FOR several reasons the relationships of syphilis to the appearance of symptoms of disorder of the central nervous system are still of considerable interest not alone because of their frequency and importance, but also because of the many interesting diagnostic problems thereby created and because of the fruitful results so often attendant upon therapeutic measures. In bringing up for your consideration today this rather timeworn subject it is not with the intention of presenting anything that could be considered as new, but rather for the purpose of pointing out again some of the doubts and difficulties which may arise in cases where syphilis of the central nervous system is brought into question.

In considering syphilis as an etiologic factor in the production of disease of the cerebrospinal axis it is necessary that we remember that although certain portions of this structure are more prone to the attack than are others, yet no part of the nervous system is exempt from the disease, and therefore signs and symptoms of a most variable character may present themselves dependent upon the location and extent of involvement. And further, the disease is not usually continuous and unbroken in its course, there occurring very frequently more or less complete remissions of symptoms associated with the disappearance of many signs, and because this happens the clinical picture may vary from one examination to another.

In more recent years it is probable that most of us have become too prone to depend upon laboratory examinations in the

making of our diagnoses, and consequently it is also probable that a careful study of the clinical manifestations of disease is not made so regularly as in the past. Take, for instance, a patient presenting certain evidences of organic disease of the spinal cord which may perhaps produce clinical pictures suggestive of two or three different tract diseases or their combinations. The laboratory commonly makes the differentiation here. In such a case it is a quite common experience that interest flags and dulls immediately upon the receipt of laboratory reports significantly positive of syphilitic infection. To be sure, there are a number of instances of syphilitic diseases of the spinal cord which previously we did not recognize as such, but which are now cleared up and made understandable by the laboratory reports. In this connection it must be remembered that positive laboratory diagnoses of syphilis do not necessarily mean that this disease is resident in the central nervous system. It must be equally well remembered that because a person has a syphilitic infection he is not immune to other diseases of the nervous system, whether these be mental or physical or whether they be functional or organic. In these cases we have to consider whether the relationship between syphilitic infection and the nervous disorder is causal or merely coincidental.

The following cases have been selected not because they are unusual and atypical, but rather because they present certain features of sufficient interest to bring them before you on this occasion.

Case I.—Cerebral Spinal Syphilis First Under Observation Ten Years Ago with Prominent Mental Symptoms and a Condition at First Suggestive of Catatonia; Positive Spirochetal Inoculations in Rabbits Made from the Spinal Fluid.—A brief of this history shows a white male, "age twenty-five, an electrician in the U. S. Navy, contracted syphilis in September, 1911. During the primary stage of syphilis there appeared a suppurating inguinal gland, which was drained. November 2, 1911 the blood Wassermann reaction (U. S. Navy Medical School) was negative. November 20, 1911 there was noted a well-developed eruption

over the body associated with arthritic and myalgic pains. November 25, 1911, 0.6 gm. of salvarsan was given intravenously, followed by marked improvement in the patient's condition. December 16, 1911 he was given another intravenous injection of 0.6 gm. of salvarsan, and on the 24th returned to duty. In May, 1912 symptoms of mental disorder developed, and he was transferred to the Naval Hospital in New York City, where the following symptoms were noted: he responded to questions slowly, attention at times being difficult to obtain, speech incoherent and irrelevant, memory poor for both remote and recent events, paresis of the muscles of the right leg, deep reflexes exaggerated, marked ankle-clonus on the right side, and Babinski reflex present on both sides. Gait was somewhat ataxic. Blood Wassermann reaction June 6, 1912 was strongly positive. On June 8, 1912 he was admitted to my service at the Government Hospital for the insane, Washington, D. C. Physical examination on admission then showed that the tongue deviated to the right on protrusion. Slight paresis of the facial muscles on the right side of the mouth, pupillary reaction normal, paresis of the muscles of the right leg, exaggeration of the patellar and Achilles' tendon reflexes, Babinski sign and ankle-clonus on the right side were present. There was no speech disturbance. Handwriting showed marked tremor. Mental examination on admission showed the patient to be disoriented for time, place, and person. There was impairment of memory for both recent and remote events. Emotionally he was happy and apparently had no insight into his condition. No hallucinations or delusions could be elicited. June 13, 1912 Wassermman reaction with blood-serum was completely positive. June 23, 1912 examination of the cerebrospinal fluid showed 510 cells per cubic millimeter, protein content markedly increased, Wassermann reaction negative. June 30, 1912 examination of the cerebrospinal fluid showed 840 cells per cubic millimeter, protein content markedly increased, Wassermann reaction negative. A portion of this specimen was used for animal inoculation. July 2, 1912 examination of the spinal fluid showed 828 cells per cubic millimeter, protein content markedly increased, Wassermann reaction

negative. On this date the patient was given an intravenous injection of 0.9 gm. of neosalvarsan. July 9, 1912 Wassermann reaction with blood-serum was negative. By this time the patient showed noticeable improvement in his mental condition, having become oriented and having gained some insight into his condition. On July 11, 1912 there was first noted a speech disturbance which progressed in less than a week to a distinct motor aphasia not associated with any marked change in the patient's mental condition. Ophthalmologic examination on this date showed the presence of a mild retinitis on both sides, hearing was normal. July 15, 1912 examination of the cerebrospinal fluid showed 151 cells to the cubic millimeter, protein content increased, Wassermann reaction negative. On this date another 0.9 gm. of neosalvarsan was given intramuscularly. On July 22, 1912 examination of the spinal fluid showed 102 cells per cubic millimeter, protein content increased, Wassermann reaction negative. A luetin test made July 28, 1912 resulted in a positive reaction. July 30, 1912 examination of the spinal fluid showed 51 cells per cubic millimeter, protein content increased, Wassermann reaction negative. Another 0.9 gm. of neosalvarsan was administered intramuscularly and the patient was given iodid by mouth and mercurial inunctions. August 8, 1912 Wassermann reaction with blood-serum was negative. August 13, 1912 examination of the spinal fluid showed 41 cells per cubic millimeter, protein content increased, Wassermann reaction negative. September 7, 1912 examination of the cerebrospinal fluid showed 18 cells per cubic millimeter, protein content slightly increased, Wassermann reaction negative. The patient now showed noticeable improvement in the aphasia condition. The right patellar reflex was still decidedly increased, and there was a very faint Babinski sign on the right side, but no ankle-clonus. There was no noticeable impairment of gait. The tongue deviated to the right on protrusion and there was still well-marked, although less pronounced, tremor shown in the handwriting. September 28, 1912 the cell count of the spinal fluid was 12.5 per cubic millimeter. Noguchi reaction faintly positive. Improvement in all symptoms had been continuous." Patient

was discharged from the Government Hospital January 8, 1913 as recovered.

Blood Wassermann in September, 1914 was negative. Examination on June 24, 1915, when he next came under observation, showed the patient was oriented in all fields, gave a good history of himself since 1911 there were no delusions or hallucinations. Insight into his condition was fair, but considering his former military rating it was considered highly probable that there was a slight degree of intellectual deterioration. There was no active psychosis. Physical examination at that time showed a well-nourished male, no atrophies or hypertrophies, no evidence of muscular weakness. There was a fine tremor of the tongue, hands, and fingers. Gait, station, and co-ordination good. At times speech seemed muffled, but nothing of a distinctly pathologic character was made out. Slight facial asymmetry. Mouth drawn to the right, tongue protruded slightly to the right, no marked facial paralysis. No ocular palsies. Right pupil was slightly larger than the left, both were regular and round in outline, reacted to light directly and consensually and to accommodation normally. Other cranial nerves negative. Tendon reflexes on the right at elbow, wrist, knee, and ankle were all exaggerated and definitely more so than on the left side, where all were also active. Babinski and Chaddock present on the right, no Gordon or Oppenheim. No pathologic toe signs on the left. Sensation to pain hyperacute generally. Blood Wassermann negative; patient would not permit a lumbar puncture.

In August, 1917, in the past several years since 1912 no treatment having been given and no new symptoms developed, the patient had some sort of attack for which he was taken to the City Hospital for treatment of a lacerated scalp and suspected skull fracture. The nature of the attack was not at this time discovered. For a day or so following his admission to the hospital he was somewhat confused and disoriented. This cleared up rapidly and he was discharged. A blood and spinal fluid Wassermann were both negative. On September 25, 1917 he had an attack, following which he was somewhat dazed and confused. He admitted then that this was his fourth attack,

the first one having occurred on August 17, 1917, and was the occasion for his being admitted to the City Hospital as above mentioned. Since then many similar attacks have been observed; they are definitely of epileptic character, but without focal signs.

There are several interesting features in this patient's condition which illustrate well certain pionts in the relationship of syphilis to diseases of the nervous system. In the first place the early incidence of central nervous system is not according to the usual rule. It is true that we now recognize that the original syphilitic infection may very soon involve the nervous system, but usually we do not see such outspoken symptoms so soon after the original lesion. This man, you will remember, was infected in September, 1911, within the usual time passing through cutaneous eruptive manifestations, was treated to a slight degree, and mental symptoms appeared the following May, or eight months later. These mental symptoms were associated with certain evidences on the physical side, namely, the weakness of muscles of the right leg with exaggerated tendon reflexes and ankle-clonus.

When he first came under my observation in June, 1912 the mental symptoms dominated the picture, and his general conduct and behavior resulting from this mental condition was not unlike that of a catatonic precox. He was stupid and dull, disoriented and inaccessible, assumed postures similar to those seen in precox. However, the underlying cause of this mental trouble became immediately apparent when the physical examination showed evidences of organic nerve involvement so suggestive of a syphilitic infection. The subsequent laboratory reports added undoubted evidence of the syphilitic origin of the clinical picture, and this, as time went on, was confirmed by the course of the disease. The laboratory reports in this case are of interest in connection with the treatment given. The unusually high cell count in the spinal fluid rapidly decreased after an initial increase, and the Wassermann became negative and so remained. Incident to the treatment both mental and physical symptoms of disease lessened, until about a month after treatment was begun, when there first appeared evidences of a

speech defect, which rapidly developed into a true motor aphasia which, in turn, on further treatment cleared up. This incident in the course of the disease was looked upon at that time as a Herxheimer reaction, and there is no reason now to assume but what that explanation was satisfactory. Another interesting feature in this case was the obtaining of positive spirochete inoculations from the spinal fluid into rabbits, interesting because at that time it was the first case of such successful inoculation on record. His improvement was such that he was discharged from the hospital as recovered.

During the next few years he was kept under occasional observation, examination from time to time showing on the physical side evidences of an old hemiplegic state which, however, was so slight that it might have been passed over had he not been under previous observation. On the mental side there was possibly some intellectual deterioration, although this could not be made apparent by our ordinary methods of examination. Judging, however, of his past rating in the Navy and the duties which he must have been required to perform with such rating, and comparing this with the present ability, the change becomes evident.

This condition ran along unchanged, the patient not taking any treatment to speak of, because being of a nomadic type he was out of reach except for occasional periods, until over five years after his treatment he again comes under hospital observation following a supposed accident and possible skull fracture. It developed later that this supposed accident was an epileptic attack, and many since have occurred without any great change in his general mental and physical condition. The blood and spinal fluid remain negative, though he has had but comparatively little treatment. The interesting feature here is that after this long period of intermission evidences of cerebral involvement shown by the epileptic attacks reappeared. We have here assumed that this epileptiform manifestation is directly attributable to the syphilis, though it is realized that you may justifiably raise a question on this point. It would seem fair to conclude that we have more than presumptive evidence for

concluding this epilepsy was syphilitic even though focal signs are entirely absent. The development of epilepsy in adult life has not been a common clinical experience, though it should be called to your attention that since the war we have met with a surprising amount of epilepsy of unknown causation, idiopathic, onsetting in adult life. Though impossible of proof, it is believed that so-called idiopathic epilepsy is a possibility further off in this case than an epilepsy associated causally with syphilis.

This man, you will remember, was discharged from the hospital as recovered and for a period of half a decade was looked upon as an example of the possibility of recovery from symptoms of syphilis of the nervous system. Such recurrence as has here happened raises in our mind question as to whether a sure complete recovery from an undoubted syphilitic infection of the nervous system can safely be predicted. To be sure, in this case treatment after the first hospitalization was given to a negligible extent, and what effect adequate continued treatment might have had in preventing the recurrence of this epileptic manifestation can, of course, be only speculative. At all events, so far as treatment is concerned, this case illustrates a too frequently entertained fallacious idea that a good course of antisyphilitic treatment given at the beginning and until laboratory tests become negative is sufficient to constitute a cure. The continuance of treatment for a period of a few months out of each year of the patient's life seems much the more rational procedure in view of our knowledge that syphilis of all diseases may remain latent in its manifestations for variable periods of time during which latency that patient is led to believe that he is well, need have no further fear of recurrence of the trouble, and with these ideas prominent before him he can see no need of subjecting himself to the annoyance and discomfort of further medication.

Case II. Organic Disease of the Central Nervous System with Physical Signs Primarily Referable to Invasion of the Lateral Columns of the Spinal Cord, Originally Looked Upon as a System Tract Disease and Subsequently Recognized as

Syphilitic in Origin. This white man is twenty-seven years old, previously was occupied as a clerk, shows in his past history measles and pneumonia many years ago, an attack of "flu" in August, 1918, chancroids in 1911, no records of injuries, use of alcohol, or drugs.

When he first came under observation a year ago examination showed him generally well nourished, height 67 inches, weight 137 pounds. Skin and mucous membranes were normal in appearance except that over the feet and ankles skin was smooth, shiny, and thin. There was noted atrophy of both lower extremities, this involving no particular muscle groups, but being rather of the character of a general wasting. The head and neck were negative, pulse 100, blood-pressure 120/65, with no organic heart disease. Lungs were negative. The abdomen was markedly prominent, this being associated with a very evident forward curvature of the spine in the lower dorsolumbar region. There was a left varicocele and in the left groin a scar resulting from a bubo incised some years back. Otherwise the general physical examination was negative. Vision was normal, but both disk margins showed a slight blurring. There was noted a coarse tremor of the closed eyelids. *x*-Ray examination of the spine showed no pathologic condition. The neuropsychiatric examination was as follows: *Cranial nerves* were all negative and normal except that the right pupil was slightly irregular in outline, both being equal in size and reacting normally to light and accommodation. *Motor system* showed considerable involvement. There was extensive atrophy of all muscles of both legs, and to a lesser degree of the muscles of the thigh. There was evident spasticity of the calf muscles of both sides, this producing a constant plantar flexion with both feet turned somewhat inward. There was marked motor weakness, more evident on the right than left side, of all lower extremity muscle groups, and there was noted also in this same distribution a coarse tremor. The patient was unable to stand without support and even then only with considerable difficulty and uncertainty. Trophic disturbances were manifested by crusts and shiny plantar surfaces, and the shiny skin of the

ankles and feet before mentioned. There was no atrophy or strength impairment in the upper extremities, but there were evident tremors of the arms and fingers. The deep *reflexes* were exaggerated in the left arm, but more so in the right. There was no wrist-clonus. Abdominal and cremasteric reflexes were absent. Knee-jerks were very much increased, this increase being more apparent on the right than on the left. Ankle-jerks were much exaggerated, with pronounced clonus. Babinski was present on the right, and suggestively present on the left. *Sensation* to touch appeared to be slightly impaired in the lower extremities, but this was variable and no definite area or marking off was possible, protopathic and deep sensibility was not impaired. Otherwise sensation was normal over the trunk and extremities. Bladder and rectal control somewhat impaired and there was reported reduced sexual function. *Psychic* examination showed no evidence of mental involvement.

With this wide-spread motor disturbance associated with a sensory disorder which was not fixed and practically negligible, and in the absence of any cerebral symptoms, a diagnosis of lateral sclerosis was made in explanation of the picture found.

It is true that the more careful scrutiny of these physical findings suggests many questions before we can accept the diagnosis as made. There are still other elements which suggest that although this may resemble a lateral sclerosis in the character and distribution of the signs, there are others which suggest as well a syphilitic cord involvement. In view of the syphilitic possibility laboratory examinations were in order. Examination of the spinal fluid showed a positive Wassermann reaction, increased globulin, and cells in the number of 69 per millimeter. This laboratory report very quickly dispels any doubt there may have been as to the syphilitic factor, but could we not have recognized this factor without the assistance of the laboratory by a more careful and painstaking clinical study of this patient?

Now, in view of these questions and taking into consideration the added information which we get from the laboratory reports, it is of particular interest that we scan the past history

of this patient for further information of possible diagnostic importance. We find that he was in good health until late in 1919, when he first noted that he would tire easily. For instance, though he had been a fairly active amateur athlete, especially in baseball, he noticed in the early spring of 1920 that a ball game so tired him that he had to quit when the game was half through. During that winter he had also noticed some visual trouble, which under treatment had been entirely corrected. In the spring of 1920 he first noticed pain in his right arm together with almost complete loss of use of this arm. This condition rather rapidly improved and, as he considered, entirely disappeared. In the summer of 1920 he was first bothered with what he calls a bladder irritation, a frequent urination. With this there was a dragging of the right foot associated with drawing sensations of the muscles of the right leg. In November, 1920 he had to give up his work because of paralysis of the right leg. This paralysis somewhat improved, so that when he came under observation at the time the examination was made, as previously given you, he complained of weakness of the right leg and difficulty in walking even with the use of a cane.

There are several points in this history which are rather suggestive. The occurrence, with comparatively slow onset, of a paralysis in a young adult is, in the first place, strongly indicative of a syphilitic etiology. Also the occurrence of visual disorders, bladder disturbance, variability in the location of the muscular impairment and its partial recovery, especially in the case of the arm, all are suggestive of the syphilitic factor. The clinical picture in so far as the distribution of the neurologic signs as revealed by examination are concerned compares fairly well with certain conditions which have been described as a primary lateral sclerosis. Also certain features of the history, particularly the character of the onset, suggest a lateral sclerosis of the primary type. The fact that the laboratory findings are positively syphilitic does not, however, finally militate against such a diagnosis, as we know far too little of the causes of the various types of neuromuscular degenerative diseases, while, on

the other hand, we do know that many of them have been found to be of syphilitic origin.

The course of the disease often gives information of considerable value, and it will pay us at this point to consider the developments in this patient within the past year. Examination at the present time will show you that he has lost weight—now weighing 120 pounds. He can walk with a cane, but uses a wheelchair much of the time. The right pupil is still very irregular in outline, and now the left is found larger than the right, though they were equal a year ago. Both respond well to light. The deep reflexes of the upper and lower extremities are exaggerated and there is a bilateral ankle-clonus. The Babinski is now definitely positive on both sides. There have been no mental symptoms. In other respects the patient has not essentially changed, and the most we can say is that there has been some improvement in his motor capacity in the lower extremities and that he subjectively feels better. In other words, you will conclude from what you have been told and what you now see that the disease has not progressed.

What may we learn from this case from our therapeutic attempts? During the past year he has been on antisyphilitic treatment a great part of the time. The lack of progression of the disease is not in accord with the usual clinical course of either a primary lateral sclerosis or scleroses incident to other types of degenerative cord tract involvements. We may be justified in assuming, therefore, that we have here to deal with a patient with spinal syphilis which has presented itself in the clinical picture of a primary lateral sclerosis, and which condition has not progressed, having been hindered in its usual or normal development by the therapy instituted. This case illustrates for you one important lesson bearing upon the effect of diagnosis upon subsequent handling. A diagnosis of lateral sclerosis usually conveys the idea of a degenerative nerve disorder of uncertain etiology and with unsatisfactory results to be expected with treatment. Should the case have been dropped at the stage of this diagnosis too quickly, having been considered useless from the therapeutic angle, and further investigation to deter-

mine the possible etiology have been neglected, the syphilitic causation would not have been found, and proper treatment could not, of course, have been given.

Case III. Case of Organic Spinal Cord Involvement for Two Years Considered and Treated as Syphilitic, and Then Recognized as a Spinal Cord Tumor, but Not Substantiated by Laminectomy.—A white male, clerk, age thirty-two, who first came under observation in September, 1919, complaining of difficulty in walking, shooting pains in the legs, sexual impotency, urinary difficulties, and speech disorder. He at that time showed a negative family history. Married, with wife and one child living and well. He contracted syphilis in 1910, having chancre and secondaries, for which disease he treated himself for about three years, taking mercury by mouth.

The present trouble dates back to about February, 1918, when he first noted that he walked with difficulty and there was a tendency to stumble. About six months later, that is, in September, 1918, he had an attack of influenza, with pneumonic involvement, following which illness he noticed a very definitely increased difficulty in walking and experienced more particular difficulty in getting about at night and in the dark. A blood Wassermann in January, 1919 was positive, but the spinal fluid examination was then negative. He was at that time given five intravenous injections of arsenobenzol and was further treated for a period of three months with mercurial inunctions. There had until that time been no eye symptoms.

Examination when he first came under observation in September, 1919 showed general physical condition poor, weight 105 pounds, medium grade scaphoid scapulæ, general physical condition otherwise was negative. Neurologic examination at that time showed Romberg present, gait was steppage of a spastic paretic character, and particularly noticeable on the right. Pupils were irregular, unequal, the right being larger than the left, they reacted to light directly and consensually and to accommodation and convergence. There was some tremor of the facial muscles and tongue on protrusion and a slight speech

defect on using test phrases. The other cranial nerves were negative. The deep tendon reflexes were all very active, the knee- and ankle-jerk of the right side being more exaggerated than that of the left. There was double ankle-clonus and an occasional right knee-clonus. Pathologic toe reflexes were present on both sides. Cremasterics were weak, especially in the right, and bilaterally the abdominals were absent. There was noted some rigidity in the quadriceps, calf, and abductor groups. There was disturbance of sensation to pin prick. Temperature, pulse, and respiration normal, urine 1010, clear, yellow color, acid, no albumin, no sugar.

During the next year (1920) he was off and on kept on antisyphilitic treatment, but without any particular change in his condition. In October, 1920 a blood Wassermann was negative, a spinal fluid Wassermann was negative, there being also a negative globulin reaction and a cell count of 7.

During the past year (1921) treatment was continued without any further change, and in November, 1921 examination showed he was unable to walk because of weakness of the legs, weight was decreased to 103 pounds, development and nutritional state poor, skin sallow, pale, pulse 96, blood-pressure 105/80, urine amber color, specific gravity 1025, acid in reaction, no sugar, no albumin or blood. Ophthalmoscopic examination showed anemia of the right disk, especially of the temporal region, the margin here being gray in color and the blood-supply reduced. Left eye showed two small choroidal patches and the blood-supply was less than the average. The field of vision showed a limitation of from 10 to 20 degrees for form and from 5 to 10 per cent. reduction for color. Pupils reacted, but the left more sluggishly than the right, otherwise were normal. Cranial nerves otherwise negative. Romberg was present, and the gait was impaired by tremors and spasticity, this being more evident on the right than on the left. Muscle power of the lower extremities was much reduced, and there was a marked mechanical irritability of the musculature of the trunk and lower extremities, with some fibrillary tremors. There was considerable atrophy of the lower right extremity and right side of

back. The reflexes of the lower extremities were markedly exaggerated on both sides. There was a bilateral ankle clonus, Babinski was present on both sides, cremasterics present and equal, abdominals elicited with difficulty. There was cutaneous hypesthesia in the lower extremities and in an area corresponding to the fourth, fifth, sixth, and seventh intercostal nerves. There was then given a history of some slight sphincteric weakness, and it was stated that sexual power had been absent for the past six months. No abnormal mental symptoms. Spinal fluid and blood Wassermann were negative, spinal fluid further showed a negative colloidal gold test, negative globulin, and a cell count of 5. *x*-Ray examination of the dorsal spine showed no pathology.

In January, 1922 the patient was again carefully investigated owing to his lack of improvement under specific treatment. Examination at this time showed that the pupils were equal in size, round in outline, reacted promptly to direct and consensual light. Ocular excursions were normal in all directions, there was no nystagmus or ptosis or difference in the size of palpebral fissures. Mouth pulled slightly more to the right in movements such as smiling. The tongue protruded in the midline, but was tremulous. The innervation of the pharyngeal muscles was intact. The motor fifth. No cranial nerve involvement was apparent. The thyroid gland was apparently normal in size, enophthalmus and exophthalmus were not present. The wrist-, biceps-, and triceps-jerks were equally and normally present on the two sides. The epigastric reflexes were both absent. The upper and lower abdominal reflexes were both absent on the left, while the upper was very faintly present on the right. Cremasteric on the left was decidedly more active on the right, but both could be elicited. There was definite clonus in both lower extremities on tapping the patellar tendon, but the clonus was more pronounced on the right. The right ankle-jerk was slightly more exaggerated than the left and the contralateral reflex in both legs took place on tapping the opposite Achilles' tendon. A definite Chaddock and Babinski were present on both sides, irritation on the right producing a general clonus in the right leg. Definite ankle-clonus was present on the right, but

not on the left. Epicritic and protopathic sensibility were normal in the upper cervical area. Cotton touch was promptly recognized over the anterior chest and abdomen, over the back, and both upper extremities. On the right side anteriorly between the fourth and seventh ribs was a zone of hypesthesia and hypalgesia. In this area there were spots of complete analgesia where the point and head of a pin were not differentiated. Temperature sensibility was found impaired in this same area, warm and cold being confused. A zone between the fourth interspace and the eighth rib anteriorly on the left side showed practically the same sensory discrepancy as was found on the right. Sensation in the upper extremities was normal. Posteriorly, beginning at the eighth dorsal vertebra and extending approximately to the twelfth on the right side, and beginning at the ninth dorsal vertebra and extending to about the twelfth on the left side was a zone showing sensory disturbances that were comparable to similar findings anteriorly. There was no hyperesthetic zone above the one described. Localization, position, and tactile sensibility were normal in both lower extremities, except that the left lower leg showed patches of analgesia and thermodysthesia of a bizarre pattern. In view of these findings a diagnosis of tumor of the spinal cord between the fifth and seventh dorsal segments was made.

Ten days later laminectomy was done, the dura being opened over the fourth, fifth, sixth, and seventh dorsal. The cord appeared somewhat smaller than normal, but otherwise was entirely negative, no tumor. There were no ill after-effects from the operation and no improvement in his condition when discharged from the hospital a month later.

This case presents several interesting features, although at the conclusion we find ourselves without any too definite an idea as to the actual pathology present. In the first place this case for over two years was considered as syphilitic, and so treated. To be sure, there are many features indicating a syphilitic element, the history and the one-time positive blood Wassermann together with the varied clinical features were strongly suggestive. However, when we scrutinize the case more carefully

it cannot be said that there was at any time sufficient evidence to show conclusively that the central nervous system was involved in this syphilitic process. The repeatedly negative spinal fluid and the absence of any neurologic signs which might not be explained by some other organic cord lesion other than syphilitic should have been given more consideration from the diagnostic standpoint. The case illustrates the point too frequently forgotten in our daily rush, namely, that a positive blood Wassermann in a person with signs of organic or functional disease of the central nervous system does not mean necessarily that such disease is due to syphilis. Another point we find illustrated in this case is the difference in opinion concerning pupillary conditions and reactions. At one time this patient was recorded as having irregular and unequal pupils, whereas two years later no such abnormalities were to be found. In this connection it must be remembered that pupils may vary from time to time, but also the personal equation of the examiner must be taken into account in pupillary or other examinations for which we have no means of accurate mathematic measurement of expression of opinions. Also the lack of response to antisyphilitic treatment over a period of years should have raised suspicion at an earlier date.

Then later, with a more rapid progression of the disability, certain more definite zonal disorders are first recorded which lead to the suspected localization in the cord. There seems insufficient reason to have regarded this disease process, local as it seems to be, as a tumor. In the first place, aside from the early history of shooting pains in the legs, there was no other history of pain such as is a frequent accompaniment of spinal cord tumors. It would seem, too, that a tumor having been present in the neighborhood of three years and of such growth necessary to produce the very marked motor disturbances, would almost necessarily be expected to produce much more wide-spread sensory disturbance than the zone above described. Just how long this localized sensory disorder was present is not shown in the record, no previous mention of sensory examination being available.

A third possibility which must be very seriously considered is a myelitic process of uncertain nature and causation, possibly syphilitic, but apparently not so. It would appear in looking at this case in retrospect that a non-syphilitic myelitis of rather chronic character would best explain the entire clinical picture and course of the disease. It is possibly in this connection significant that this patient, though he complained of difficulty in walking previous to an attack of influenza and pneumonia in late 1918, nevertheless following this infection his symptoms became much intensified and continued to progress. To be sure, this may have been at one time syphilitic, though there is no evidence of this other than that of coincidence. It should be remembered in this connection that the spinal fluid examination was not made until long after the man had had antisyphilitic treatment and, therefore, possibly thereby made negative. At the operation, though no tumor was found, it was noted that the cord appeared distinctly smaller than was normal, and this may have resulted from a degenerative process secondary to a more acute myelitis at the beginning.

This case illustrates the possibility of error in concluding that a syphilitic nervous condition exists, basing such conclusion too largely upon the history and positive blood Wassermann and giving too little regard for the likelihood that other diseases than syphilis produce organic changes in the central nervous system. As a result in this case antisyphilitic treatment was carried on in a rather uncritical fashion for a long period and without satisfactory results.

In conclusion, the oft-repeated statement may be again dragged in for final emphasis. Syphilis affecting the central nervous system may produce clinical pictures which are on casual examination most easily confused with almost any other disease of the central nervous system, and some of these even after the most careful study and investigation cannot be distinctly and definitely differentiated as syphilitic from the disease which they simulate. It is a safe rule that wherever there is a possibility of an underlying syphilitic factor in the etiology of any disease of the central nervous system adequate treatment for

this syphilitic factor should be given. If properly done it is quite certain that it cannot cause harm, and there is always a chance that much good to the patient may result. As a last note it may be said that the therapeutic test is not ultimately final, and because a patient supposedly syphilitic does not respond to antisyphilitic measures it cannot be certainly concluded that syphilis is absent.

CLINIC OF DR. SIDNEY I. SCHWAB

BARNES HOSPITAL (WASHINGTON UNIVERSITY)

FIVE CASES FROM THE NEUROLOGIC CLINIC OF BARNES HOSPITAL

I PROPOSE to show in this clinic how the recognition of a clinical picture may produce difficulty in differential diagnosis through the introduction of a freshly grouped set of diagnostic items. The more accurate the knowledge of a newly recognized disease becomes, the more necessary is it to re-examine some of the data upon which diagnostic conclusions in reference to other conditions have been based. The newly recognized condition which is constantly upsetting our diagnostic complacency is encephalitis lethargica. It is this disease of the nervous system which has infiltrated into the diagnostic problem presented by three totally different conditions; disease pictures which have often been diagnosed with apparent ease. These three diseases are brain tumor or abscess, syphilis of the nervous system, and meningitis of various types.

In the light of recent experience it is increasingly clear that instances belonging to these groups have been wrongly interpreted because the possibility of their being encephalitis has not been constantly kept in mind. The cases presented this morning, therefore, are grouped about a diagnostic center—held by encephalitis. It is this position which will be primarily attacked from the point of view of its exclusion or inclusion. When this has been done the diagnostic pathway should not be very much obstructed or, at least, the final goal of accurate diagnostic conclusion is clearly in sight and ultimately may be reached. It is pertinent to say a word here concerning neurologic diagnosis particularly as it reflects directly upon the problem presented by

these cases. From the data obtained from the story of the patient, his personality, family, and environmental factors, and from the physical and laboratory examinations, deductions of a neurologic kind are drawn. Such deductions must be courageously followed to the final conclusion, which is the diagnosis. In reaching the final explanation knowledge, experience, and intuition are important factors. They must be used, however, without prejudice to the facts obtained in the study of the case. Observed facts and the anatomic data should not be dodged, because the correct therapeutic attitude toward the condition presented by the patient depends in many neurologic cases primarily upon the diagnosis arrived at. In all organic diseases of the nervous system localization is of the greatest significance, and the response of the nervous system to disease is always bound up with the element of locality. In the problem presented by encephalitis and its relation to brain tumor this will be given its due emphasis. The correct interpretation of this feature is the key to the solution of the intricate problem presented by the four diseases which form the subject of this clinic. The fact that in some instances what appears to be wrong diagnoses have been made illustrates two phases of the problem presented. One is that diagnostic deductions are not as accurate as they should be, and second, the limit of surgical exploration with the object of safe-guarding the patient prevents the complete examination of that portion of the brain to which the diagnostic deduction leads. Therefore this clinic must be looked upon by you not only as a demonstration of a series of interesting cases but also as an exercise in diagnosis. Diagnosis in this sense means simply the utilization of all the important data that can be derived from the examination of a patient plus the most logical interpretation of that material for the purpose of identifying the disease in question and pointing out the way toward proper treatment.

Encephalitis becomes a source of confusion because it can produce clinical pictures which simulate any or all of these three conditions with striking exactness. It also may be associated with laboratory findings or their absence which are compatible with those found in any of the three conditions mentioned. In

addition, encephalitis often in its acute phase may be grafted on an old syphilis or upon an abscess or tumor of the brain which has not been recognized before.

In the selection of cases for this clinic I have avoided typical or text-book-like examples of the conditions under scrutiny, and have chosen those that have come into the neurologic clinic in the routine of its activities. They are of the borderline type, presenting a confused picture made up of various symptoms and findings found in any of the conditions. Variants and differences rather than similarities or likenesses are the characteristics of actual experience with people whose nervous systems are the subject of disease. Therefore such a clinic as this is a replica of the daily experience and daily contact with the actual problems as seen in hospital, dispensary, or practice. The symptom which is found in all of these conditions and which is a presenting cover for the whole group is that disturbance of consciousness called lethargy, stupor, or apathy, or the dulling of response to environmental stimuli of any kind. This may be called the common denominator of the four conditions here about to be studied, and in many instances it is this symptom which brings the individual under neurologic scrutiny. Of lesser significance, perhaps, but still common to all of these conditions, is the complaint of headache or some disturbance associated in the mind of the patient with this term. In all of these conditions mental abnormalities of many sorts may be found. These vary from simple disturbances of intelligence, in the way of slowness of mental process, slight loss of memory, defect in disorientation, to complicated abnormal states in which confusion, delusion, and hallucination are found.

As the purpose of this clinic is to bring into the category of these three diseases that of encephalitis, it will be necessary to exclude this condition before going further in the selection of one or some of the three remaining. Only such cases have been chosen, therefore, which presented in the first instance some of the symptoms associated with encephalitis lethargica. In 2 of the cases presented it will seem to you perhaps that dragging in encephalitis is rather artificial, and that without its exclusion a

diagnosis could have been made just as well and with just as much safety. It is, however, a principle of clinical demonstration to bring in factors which would seem to have an exaggerated emphasis in order to properly accentuate the point at issue, and it is only by guarding against the omission of this tendency that mistakes in diagnoses in the long run can be avoided. In other words, it is essential at the present time in all cases which present primary symptoms of lethargy, stupor, or coma, developing either acutely or chronically, to consider among the first possibilities that of encephalitis.

The students presenting these cases will give a brief clinical résumé and the important laboratory and other findings with the purpose of indicating the problem of diagnosis and furnishing facts for the solution of the problem. Comment and discussion will be based on data so presented. The complete story of each patient is given, even if it was not known at the time of the presentation of the case.

Case I.—The first case is one of syphilitic meningitis which developed acutely after a very brief interval had elapsed following the initial infection. The primary lesion was extragenital. One interesting feature of this case is that he was first seen by a neurologic surgeon for what was supposed to be brain tumor. This patient is twenty-four years of age, and came to the Out-patient Clinic September, 1921, with a complaint of sore finger. The history of this sore finger is important. A pimple appeared about three weeks before, which was opened with a needle. Healing did not take place, and on examination in the clinic a general macular eruption was seen. For the first few days there was a history of chills and fever. Blood Wassermann was found strongly plus, and a diagnosis of syphilis in the eruptive stage was made. After a number of days of headache and general malaise routine antisyphilitic treatment was begun. On October 26th he became hemiplegic and then unconscious, and three days later he was brought into the Barnes Hospital in a deeply stuporous condition. The following diagnostic possibilities were noted: Brain tumor, encephalitis, and

meningitis. Lumbar puncture done immediately after entrance cleared up the diagnosis. There were 385 lymphocytes and a 4 plus Wassermann both spinal fluid and blood. A note made November 1st brings out clearly the diagnostic problem. The picture is one of meningitis with marked intracranial pressure. Although syphilitic meningitis seems the most probable diagnosis, the possibility of meningitis and encephalitis should be considered. The patient was then transferred to the Out patient Service, where a more intensive type of treatment was carried out. He improved somewhat, and on the 17th or 18th of December was readmitted, with the important finding of choked disks in both eyes. Lumbar puncture still showed large numbers of cells and the usual findings in syphilitic fluids. Under treatment the choked disks subsided, the acute meningitic reactions grew less, and the patient returned to his work as a mechanic in a garage with no important residual symptoms or findings, except an increased cell count and a slowly receding Wassermann reaction in fluid and blood. There are several important comments to be made in this case. It is unusual for the nervous system to respond so quickly and energetically to syphilis and to show such an elaborate meningitic display in consequence. The hemiplegia, the stupor, and the choked disks are so characteristic of cerebral tumor located in the motor area that without the laboratory findings an operation might well have been undertaken. The suddenness of onset recalled the possibility of encephalitis very strongly, and in the midst of an epidemic of this disease such a case as this may easily be incorrectly diagnosed. Response to treatment was striking, and chiefly so, I think, because it was planned along very conservative lines. Acute syphilitic meningitis in which the spinal fluid cell count reaches high numbers should be treated by small doses of salvarsan and carefully regulated deep mercury injections. Salvarsan injections, too frequently repeated with large dosage, causes, in our experience at least, violent reactions which may be dangerous to the patient, leaving permanent residual effects of a serious kind. In this case at the present time, although you see very little trace of the source of acute illness, the clinical

picture presented by the patient when he first appeared in the wards of the hospital showed a most intense reaction on the part of his nervous system. Not only did he present a picture of an acute illness of a serious kind, but so marked a condition of stupor, confusion, and loss of environmental reaction that any of the four conditions which are the subject of this clinic might well have been considered as a possible explanation. The fact that the cause of his mental state and the condition found in his eyes were adequately accounted for through the examination of the blood and spinal fluid would not remove such a case from the possibility of encephalitis. In fact, one of the most common and most definite symptoms in an acute encephalitis is just such a disturbance of consciousness as this patient presented. The case is shown, therefore, in order to point out the necessity of carefully considering the factor of this disease in states similar to this.

Case II.—This case was brought into the hospital from a distant city in a condition of deep stupor out of which the patient at times could be aroused, but with great difficulty. This is a woman fifty-four years of age, whose present illness begins about three or four weeks before admission. The first evidence of illness was a severe supra-orbital headache and complaint of dimness of vision. The attending physician thought that the symptoms were the premonitory evidences of influenza, and so treated the case. Up to the present attack the patient had had no important disease of any kind. She was a very active woman, the head of a household, and was regarded by those who knew her and those about her as being an exceptionally vigorous woman both physically and mentally. When the patient was first put to bed a blood-pressure of 178/90 was found, but after three days' rest in bed the blood-pressure was 144/86. The initial rise in blood-pressure was reported by the physician who had had charge of the case, and was never afterward found in the subsequent study of the case at the Barnes Hospital. For ten days after the beginning of her present illness there was a constant but slight rise of temperature, the highest being about

101° F. and the average being between 99° and 100° F. The temperature curve within these narrow limits, however, was very irregular and showed no tendency toward the typical curve associated with common infectious diseases. Such findings as were discovered in the primary treatment of this case at her home were suggestive of some acute infectious process which presented no alarming features to the physician who was in charge. About ten days or so after the initial symptoms, that is, on February 23d, she began to show the first evidence of a serious complication on the part of her nervous system. A slight weakness of the left arm was noted, and soon after this the left leg also became weak, and a mild degree of anesthesia on the paralyzed side was found at examination. Deep reflexes disappeared completely, and with this there developed incontinence of the bladder and to some extent the rectum. With the development of these symptoms one after another the nervous system appeared to be involved without much question, and when a mild degree of optic neuritis was found by the ophthalmologist, who was called in consultation, the clinical picture began to take on the definite characteristics of an involvement of the central nervous system as a part of or in consequence of some acute infectious process. A lumbar puncture showed 10 cells with no increase in globulin and negative Wassermann. Throughout the whole primary period of this patient's illness there were remarkable periods of alternating stupor and partial and complete return to a normal state of mind. At that time this feature, that is, the stupor or lethargy, was the most outstanding feature of the case and seemed to impress the physician in charge more than any other thing. The weakness of the left arm and leg were regarded by him as of secondary importance, showing as they did that there must be a lesion on the right side of the brain. The family physician was much impressed with the curious and paradoxic feature presented by the alternating lethargy and mental alertness which the patient presented. It seemed to him, and rightly I think, that this was not a part of an ordinary cerebral process due to hemorrhage, embolism, or thrombosis, but seemed to have some relation to the fundamental condition which had

attacked the patient and of which the paresis of the left arm and leg were recognized symptoms. The patient accompanied by the family physician then came to the Barnes Hospital and entered the neurologic service on March 5th, that is, about four weeks after the beginning of her illness with the history as outlined above. On admittance she was stuporous and hemiplegic and a marked degree of optic neuritis was discovered at first examination. On the next day the patient was conscious, fairly orientated, and could answer questions promptly and intelligently. Periods of stupor intervened during the day, out of which the patient apparently could arouse herself and showed a fair degree of orientation, interest in her surroundings, and could recognize and call by name some of those about her. A note by the ophthalmologist on this day confirmed the admission report on the eye-grounds, and the optic neuritis with a questionable beginning choked disk was certified to by him. The diagnostic possibilities at this stage were encephalitis, brain tumor or abscess, and meningitis. The question of a vascular lesion in the capsular region was carefully discussed and excluded on account of the disk changes and alternating mental state and the absence of vascular lesions elsewhere. The patient was not particularly arteriosclerotic and there was no reason to suppose that a vascular condition of the nervous system could be responsible for the symptoms which this patient presented. The neurologic examination determined the presence of a left-sided paresis, but did not show the sensory changes previously found. Some voluntary movement of the left leg was present. Neurosurgical consultation was confirmatory of the diagnostic conclusions before reached, and no operative procedure was advised on account of the fact that some of the mental symptoms appeared to be clearing up and the fact that a diagnosis of encephalitis lethargica offered the most convincing explanation. There developed soon after admission a curious feature which it is of interest to call to your attention and which is present in some degree now as the case is presented. Upon admission it was noted that the slightest exertion caused a rapid rise in the pulse-rate. When the patient is turned over in bed or manip-

ulated for examination purposes a remarkable rise in pulse rate is found. Along with this increase in pulse rate an irregularity in respiration developed, together with a marked duskiness and cyanosis of the face. The first red blood counts were between 5,000,000 and 6,000,000. As soon as this duskiness and cyanotic appearance of the face were noted a routine blood examination was done every few hours. The red counts steadily arose to over 7,000,000 on the fourth day of the patient's presence in the hospital. The leukocyte count varied from 17,000 to 26,000. It appeared obvious that here was a condition of temporary polycythemia following in the wake of a central lesion in which the respiratory mechanism was probably affected. There is ground for believing, therefore, that there was some vagus involvement due to the spreading of the lesion from its original focus.

The differential question at this period might be stated in this way. The important possibilities are encephalitis, brain abscess, or tumor. There has been a marked tendency toward temporary clearing up of the lethargy during which the patient speaks clearly, asks for things, recognizes those about her. During the examination this morning, which was five days after admission, patient could carry out orders, put her tongue out, etc. Very soon after she sank into her customary stupor. The increasing leukocytosis and the polycythemia become now the outstanding features. There was no unusual rise of temperature at this time nor increase in her heart rate when the patient was at rest. It was difficult to associate an abscess or tumor with this curious combination of symptoms. In encephalitis, with its irregularity of disturbances and basal ganglion predilection, sufficient interference in respiratory regulation could be produced to account for the polycythemia. A lumbar puncture was now done. The findings here exclude meningitis, there being only 5 cells in the fluid and negative Wassermann, no increase in globulin. The colloidal gold curve was flat, but sugar contents of the spinal fluid was high—0.077. It is important in the further description of this case to especially note the high sugar in the spinal fluid. Blood-sugar taken at this time also showed

a high percentage—0.135. On March 11th, five days after admission, significant changes were found in the neurologic examination. Pupils suddenly became dilated and at times irregular, and also a slight difference in size of the two pupils was found. Definite spasticity developed in both legs and a questionable Babinski showed itself on the right, and ankle-clonus was found present on the left. The spread and change of findings was interpreted as indicating that the encephalitic process was attacking midbrain structures and influencing the static process by irritation phenomena. From this stage on patient showed little change except such as might be produced by steady progression of lesions. Her breathing became increasingly difficult, swallowing interfered with, cyanotic attacks developed, and the patient died the ninth day after admission. A spinal puncture made immediately after death showed 15 leukocytes, with sugar as high as 0.099, and the spinal fluid curve, which in the first instance was confusing, now showed clearly in the meningitic zone. Autopsy was refused. The subsequent history of this case, which is given here following the presenting of the case in its primary stage at the former clinic, gives a complete story of the present illness up to the death of the patient, but without an opportunity to confirm or deny some of the diagnostic possibilities which this case at its early presentation showed. The most important single series of laboratory tests were those which were made upon the spinal fluid immediately after death. This spinal fluid was taken a few minutes after the patient died, and therefore cannot be said to have been influenced by potsmortem changes of any sort. The increased number of leukocytes and high sugar content of the spinal fluid and the curious alteration in the curve seemed to furnish the necessary support for the diagnosis of encephalitis lethargica which was made during the life of the patient and for which the subsequent course of the case was fairly characteristic.

Case III.—It is only recently that epilepsy or, rather, epileptic convulsions have become symptomatically associated with encephalitis. In this way another diagnostic item has infiltrated into that complex problem. Nothing in the way of interpretative

questions has interested the neurologic service the last two years more than adult or acute epilepsy. The term as here used means the appearance of convulsions of an epileptic type in an adult free of epileptic inheritance with no previous experience with epilepsy, and with nothing in the past history to furnish any etiologic factors for its appearance. A sudden convulsive seizure in such an individual immediately brings up the possibility of tumor, abscess or meningitis. Of great importance in the latter diagnosis is the syphilitic type. It is, in addition, necessary to study such a case from the point of view of an encephalitis, and it is from this angle that the following should be viewed. The assumption is that in an acute epileptic manifestation in an adult something new in a pathologic sense has happened to the nervous system, and the changes so produced must be looked at as of great importance in the causation of epileptic manifestations. This possibility does away with the necessity of regarding an epilepsy of this sort as some kind of mysterious functional reaction on the part of the nervous system, and impels every student of such a case to a renewed effort to find a material basis for the disease in question.

A woman, age forty-two, married, with children was brought into Barnes Hospital in a deep stupor, out of which at that time she could not be aroused. The stupor was so profound and the loss of consciousness so deep that the term "coma" could be more properly applied in describing her condition. Temperature on admission was about 102° F., respiration and pulse in proportion. The immediate history shows that after lunching at one of the down town clubs, as she was shaking hands with a friend she suddenly felt a severe pain in her head and began to feel very weak, so much so that she seemed about to faint. She was helped to a couch and immediately lapsed into a state of unconsciousness. When her husband arrived a few minutes afterward the patient was conscious, but irrational and disorientated. She was then taken to the office of the family physician, and while on the way in an automobile had a typical epileptic convulsion, followed by a second while in the doctor's office, and a third after admission to the hospital. All the con-

vulsions were similar to those seen in epilepsy, and as such must be considered as the chief presenting symptom indicative of some acute pathologic process that had developed within the last twenty-four hours. The past history of this patient showed nothing that threw any light on the sudden appearance of this convulsion. While she had never been a very vigorous woman and had had many experiences with sickness of various kinds, she had never had any of the infectious diseases or traumatic factors commonly related to convulsive seizures.

The first thing considered naturally was the possibility of the convulsions being caused by food poisoning. Her stomach was washed out, but no residue found, and nothing at all suspicious in the stomach washing. No other member of the luncheon party was sick, although they had all partaken of the same things that this patient had eaten. This explanation, therefore, must be excluded at this point.

The leukocyte count was up to 20,000 on admission and continued so until a week or so before discharge. A slight rise in temperature was present until the last few days of her stay in the hospital. The leukocyte count and temperature remained as probable indications that some acute infectious process had developed out of which as one manifestation the epileptic-like attacks had come. This patient was under observation and study for two weeks. No more convulsive attacks were seen, and after a period of variable and intermittent mental confusion, lethargy, disorientation, she cleared up, became much stronger, and left the hospital very much improved.

The question that now comes before us is that of the interpretation of these acutely recurring epileptic-like seizures in the presence of an acute febrile process, obviously of an infectious type. Keep your attention focused on the possibilities—tumor of brain or abscess, meningitis, or encephalitis. The physical examination of this patient was, in the main, negative, at least it may be called so in so far as it might have thrown light on some of the things causing convulsions, such as nephritis, cardiac disease, hypertension, etc. All such factors were completely excluded by the array of negative findings, both physical and

laboratory. Examination of the nervous system showed very little out of the way and nothing of a gross nature. There were, however, several rather minor findings that are suggestive, and point to a possible pathway of escape from the diagnostic dilemma which this patient presented. An inequality of pupils, weakness of the seventh was noted from time to time, and an absence of changes in eye-grounds. One lumbar puncture was done under gas anesthesia, but only 2 cells found. Spinal fluid was normal, blood-sugar was high—0.138, Wassermann negative, as were also all laboratory, *x*-ray, and cardiographic studies.

The epileptic seizures in this case must be looked upon as symptomatic, as an indication of something new having taken place that has disturbed the normal inhibitory mechanism of the brain as to cause the convulsions or, at least, to cause that type of reaction. The temperature and leukocytosis are suggestive of an infectious process. Such a process in the absence of other evidence pointing to a meningitis, abscess, or tumor and not associated in any way with evidence of an infectious disease elsewhere has much to indicate encephalitis lethargica. Abscess, brain tumor, and meningitis are amply excluded by the array of negative findings, and by the evidence at hand that an acute process is associated in some way with the appearance of the convulsions. Nevertheless, brain tumor, especially with frontal lobe localization and abscess, were continually kept in mind. The most important feature of this case has not to do with the minor findings in the nervous system or the slight deviations from the normal in the general physical examination, but in the mental state which she showed at admission. The state of apathy noted was followed by restlessness. There was a marked deviation from time to time in the mental state of this patient. At times she would be singularly alert, noticing and being interested in her surroundings, and at other times she was in a state of somnolence and apathy. At such times she appeared as though she were in a deep and quiet sleep. When aroused from this state, which could easily be done, the patient was immediately aware of her surroundings, was orientated completely as to time and place, and realized all the necessary

conditions of her stay in the hospital. As soon as she had answered questions and apparently satisfied inquiry directed to her she would fall into a state of lethargy and remain in this state until again aroused. This is so typical of the lethargy of encephalitis that a diagnostic chance could be based upon this phenomenon alone. The occasional and episodal and transient findings in the nervous system, such as pupil difference plus deep reflexes, ankle-clonus, slight weakness of the seventh nerve, are all characteristic of the reactions of the nervous system to the encephalitic process. The fact that none of these things were permanent and that none of these findings lasted longer than a day or so and often only a few hours lends an additional bit of evidence to the diagnosis of encephalitis.

The history of this case after the patient left the hospital is of some interest as showing how warranted the diagnosis of encephalitis at that time was. For some weeks after the patient was discharged from the hospital she appeared to be very well, gained some weight, and apparently was in the way of regaining some of her former strength and vigor. Owing to some disturbance of digestion the patient was under the care of a gastroenterologist and had been put on some sort of diet. Without any particular warning, when the patient seemed to be in a fair condition, she lapsed into a state of unconsciousness and after three days she died. I saw the patient in consultation twenty-four hours before death and nothing could be made out at this time that would throw any light as to causation, and it seemed quite probable that she had succumbed to a recurrence of the same process for which she had been sent to the Barnes Hospital. This is by no means an uncommon occurrence as a consequence of encephalitis lethargica, and in more than one instance a similar incident has come under our notice.

Case IV.—The fourth case is presented with the idea of bringing out clearly a new phase of the diagnostic problem in cases of this kind. The difficulty in this case is caused by the appearance of a set of symptoms which have so definitely a localizing significance that a well-marked and definite cerebral

lesion could be diagnosed, and for the relief or cure of this condition a cranial operation was advised and carried out. It, however, did not disclose the lesion that was suspected. The question of frontal lobe tumor is in this way brought to your attention and an opportunity furnished to discuss the similarity between frontal lobe symptoms and mental abnormalities seen in encephalitis. This case is a woman, fifty-five years of age, a widow who was sent to the hospital by a neurologic colleague. She was brought in an ambulance and when first seen in the ward was in a state of complete coma. Previous history has reference to numerous nervous breakdowns, culminating in a very severe one two months ago. This may be taken as the initial phase of the present illness. The day before entrance to the hospital the patient suddenly became comatose. Although for the last two months she had been complaining of her usual nervous symptoms, she had been up and about following her trade, that of dressmaker. The most significant item in the past history has reference to her husband's death in an insane asylum from paresis, or at least this diagnosis was made at the time of her husband's death. When the patient was first seen she had come out of her coma to some extent. She understood simple questions, but showed evidence of speech defect, her voice was nasal, and the words were pronounced uncertainly, with a definite slurring and clumsiness in word expression and sentence formation. The speech defect was not unlike that seen in paresis. The significance of this was no doubt emphasized and perhaps exaggerated to some extent by the history of her husband's disease and its outcome in the sanatorium. There was found also at the first examination a definite left facial paralysis with marked overaction of the right facial. Owing to the history in relation to her husband, the first explanation of this patient's condition was that she had a paretic seizure followed by intense stupor. An immediate spinal puncture was advised and carried out. The blood and spinal were both negative as far as Wassermann tests were concerned, cell count 9, colloidal gold curve not characteristic. This curve could not be used in a direct diagnostic way. It was felt, however, that it

could be used as part of the excluding data of paresis. It was now assumed after a number of examinations that there was a more sharply localized cerebral lesion than was at first thought likely, especially as the general physical and laboratory study showed nothing in the way of a process that might account for the symptoms of stupor and apathy. A slight but transient cranial nerve involvement and a slight and persistent rise in temperature was always present. Kidney function, heart, and lungs were negative. The patient showed a constantly changing mental condition from one examination to another. In addition, she was often drowsy and confused. Toward the evening of the day this note was made the patient became deeply stuporous and could be aroused only with the greatest difficulty. A right facial and left third now made their appearance, with a questionable Oppenheim in the right leg. Cranial nerve findings were never definite and often evanescent. The irregularity in the mental symptoms were most striking. Alternation of deep drowsiness with a considerable degree of alertness pointed to the possibility of a lesion of the frontal lobe. The *x*-ray of the head presented supporting evidence, as there was found a pyriform shadow which seemed to be on the right side of the median line. The facial weakness now appeared on the left instead of the right, and it occasionally became quite marked. A slight but definite blurring of the disks could be made out. This did not seem to advance to a complete picture of optic neuritis. About this time the patient began to clear up mentally, appearing more alert and better oriented. The facial weakness which had been noted on several previous examinations had almost completely disappeared, the gait improved, and speech showed much less disturbance on the whole, although, curiously enough, the defect became more marked with the increasing alertness of the patient. That is, when she became more responsive to environment and talked more the speech defect seemed more pronounced than when she was in an apathetic or stuporous condition and speech was more limited. The neurosurgical consultation called attention to the speech defect and the curious alternation between the right and left

facial. The visual fields showed no defect of importance. On account of the difficulty of cerebral lateralization, ventricular air injection was done, and the plates so made were studied. A diagnosis of obstruction of the foramen of Monro or occlusion of left ventricle was noted in the *x*-ray interpretation. The anterior portion of the left ventricle was collapsed and the posterior horn showed definite deformity. The patient was now regarded as a neurosurgical case and was transferred to that department, with a diagnosis of left frontal tumor, based upon two sets of observed data. The presence of the right facial weakness, clonus, and Oppenheim, right, weakness of the right arm, and definite but temporary ataxia, and the *x*-ray findings. The second group of facts were the mental symptoms that had been present ever since entrance: disorientation, stupor, dulness, apathy, with intervals of alertness. The episodic character and sudden changes in the mental state have been very striking. At no time has complete return to normal taken place. There has been considerable mood variation, and a slight degree of euphoria has been almost constantly seen. Insight has been defective, patient has only a slight notion of the relation of an operation to her mental state, and although she expresses fear of an operation, she cannot be made to feel the seriousness of her condition. The speech defect is difficult to interpret—it is not aphasia, but is much more in the nature of a wide-spread intellectual defect. Mental intelligence tests with analyses of the deviations supports this view. The patient was explored on the left side in the region between the motor area and the tip of frontal lobe. Nothing abnormal was found. Patient was discharged from the hospital in good condition, slightly improved, but died about four or five months later. No autopsy was obtained.

Case V.—The last case that I shall show is one of abscess of the cerebellum. This is demonstrated chiefly to bring out the curious mental symptoms which were present, so that it will be clear to you that even in so sharply localized a lesion certain phases of the symptomatic reaction call to mind the picture

that is often seen in encephalitis and also in frontal lobe processes.

This young married woman, twenty-four years of age, came into the ward with a diagnosis of spinal cord tumor, which had been made by her own physician. While this diagnosis was not substantiated by the study of the case at the hospital, it was no doubt based upon findings which in the beginning of this patient's illness were difficult of interpretation. Her chief complaint on entrance to the hospital was diplopia and failing vision, and the chief admission finding was a marked choking of both disks. The past history, as far as general illness is concerned, was not important, with the exception of a surgical experience some short time before. In October, 1921 the patient had an ovariotomy and appendectomy done. The only other item in the past history which might be of importance in connection with the present condition is a history of two attacks of gonococcal infection—one seven years ago and one five years ago. The abdominal operation was carried out in a hospital where this patient lived, and was uneventful as far as the surgical aspect of the case was concerned. About two weeks, however, after the abdominal operation, while still in the hospital, she had an attack of double vision. This lasted about two weeks and then apparently completely disappeared. In November, however, the double vision again appeared and has persisted ever since. She left the hospital and in January, 1922 began to have severe temporal headaches. These headaches were often accompanied by sharp pain in the back of the neck, which radiated toward both shoulders, and was, according to the report, very severe. Following the headaches attacks of vertigo began, accompanied by weakness, rapid pulse, and considerable degree of anxiousness. Difficulty in walking and great dizziness now developed and became progressively worse. Such were the complaints and symptoms and past history of this patient upon her entrance into the neurologic service. The most outstanding feature of the examination on admission was the choked disks which has been referred to. The choking of the disks was very marked and there was a good deal of infiltration and edema

around the edges. There was a bilateral paralysis of the sixth, more marked on the left than right, cerebellar type of gait and station, rapid pulse, and a curious state of euphoria, which were the outstanding features of the admission examination. A subsequent examination showed, in addition, a marked nystagmus and diminished conjunctival and corneal reflexes. As the case was studied and as you can observe now the mental condition is most striking. She has been always euphoric; smiling and laughing and joking most of the time in spite of pain, dimness of vision, inability to sit up, inability to carry out any co-ordinating movements, and with the prospect of a serious operation and a serious diagnosis before her. When she is questioned about these things she replies in an apathetic and indifferent fashion, smiling constantly and apparently not at all impressed with the fact that she has a tumor of the cerebellum and that treatment for this tumor is a serious operation. These facts were discussed freely with her, and although she understood perfectly well what the condition was, her reaction to it was most illogic. Very frequently she would laugh without apparent cause and regarded the whole affair as though it were a joke. The exaltation of the patient was so marked and her apparent illogic attitude toward her disease so unusual that a mental test was made for the purpose of finding out whether characteristic reactions to a frontal lobe tumor could be found. However, there was nothing in this test that gave any grounds for considering any other localization than that furnished by the objective findings pointing to the left cerebellum. The constant presence of weakness of the left seventh of a peripheral type was a most important outstanding feature toward the lateralizing process to the left. Syphilis and other causative factors were excluded by examination of the spinal fluid and blood. An air injection of the ventricles was carried out and the plate showed both ventricles dilated. In spite of the negative results of the air injection it was felt that there was sufficient lateralizing information present in this case to determine that the left side was involved. The patient was then transferred to the neurosurgical service and an abscess was found at operation in the left cerebellar lobe.

Pus was evacuated from this abscess, leaving a cavity about 3 inches deep. Patient died some weeks later, and autopsy confirmed the original diagnosis of left cerebellar abscess without revealing the source of the infection. Permission for complete autopsy not obtained.

The case is of value, therefore, in calling attention to the fact that a sharply localized cerebellar lesion, successfully explored and certified to by operation, can produce some of the mental anomalies and psychical peculiarities of a lesion usually associated with frontal lobe, and that the mental picture presented by the patient is such that in considering all possible explanations that of encephalitis should be likewise thought of.

In reviewing the 5 cases that have just been demonstrated, and particularly noting the outcome in some of them with particular reference to what appears to be in one instance a false interpretation of the facts obtained by physical and neurologic examination, the features common to all these conditions must have struck you. There is perhaps no condition in the ordinary practice of medicine which presents such an intricate group of possibilities as that of such a disturbance in consciousness that the patient is unable to give any information about himself and is therefore unable to co-operate in the ordinary technic of examination. The stupor and coma and such other disturbances of consciousness that come under these terms in a quantitative or qualitative way are to be regarded, first, as the evidence of a more common type of disturbance than has been here demonstrated by these cases. After the possibility of head trauma, nephritis, ordinary poisoning, intoxication, infectious diseases associated with high temperature, and mental conditions such as dementia præcox and hysteria are considered, then the question of a definite lesion of the nervous system must be gone into. Very frequently the solution of the problem can be obtained by a proper study and consideration of the findings shown by neurologic examination. There is no question but that, at the present time at any rate, among the possibilities most frequently met with is encephalitis lethargica. Many a difficult diagnostic problem will be successfully solved if the patient is

examined from the standpoint for which these cases have been demonstrated. The fact that encephalitis cannot be diagnosed at the present time upon any set of specific characteristic reactions makes the intrusion of this disease into the diagnostic question most opportune, and in no instance of the sort that has been here shown should the possibility of encephalitis be left out of the question. This clinic, therefore, will have served its purpose if the question of excluding or including encephalitis in such types of cases should become a routine matter.

CONTRIBUTION BY DR. ELSWORTH S. SMITH

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ACUTE INTERMITTENT CARDIAC DECOMPENSATION[1]

THE efficiency of the heart as a mechanical pump depends, first, on the integrity of the cardiac muscles as a pumping force; second, on the pressure within one or several of the cardiac cavities to be overcome by this pumping force.

The integrity of the muscles of the heart may be directly affected by certain toxins, as in the infectious diseases, or through malnutrition, as in disease of coronary arteries, in the anemias and cachectic states; or they may be indirectly affected through any agency which increases the pressure within the cardiac chambers. This increase in pressure results mainly from valve lesions or from arterial hypertension.

The condition of increased pressure within the cavities of the heart calls for increased work on the part of the organ, which is met, if the increase in pressure be sudden, by dilatation of the involved chamber, and should this increase in pressure be brief the heart muscles through their reserve force may more or less promptly restore the normal size of the affected cavity with removal of the heart strain, but should the pressure be sudden, severe, and prolonged, its reserve force may be unequal to the sudden demand, and the strain may at times be permanent, leaving the individual, before healthy, now a hopeless cripple from permanent cardiac weakness. Where the increase of pressure within the cardiac cavities develops more gradually, there results more or less dilatation with accom-

[1] I wish to acknowledge my indebtedness to my associate, Dr. N. N. Shackelford, for much valuable aid in the collection of data from our records.

panying hypertrophy, and through this increase in the muscle mass the organ is enabled to meet the increased work demanded of it, and so long as its muscles are in this way equal to the task, so long will the individual be comfortable, he having then, technically speaking, a compensated heart.

This condition of cardiac compensation unfortunately cannot be indefinitely maintained, for sooner or later there develops, as in all overworked muscles, muscle fatigue consequent on certain changes in the muscular tissue, resulting either in fatty degeneration or chronic myocarditis.

In a certain proportion of cases, according to Osler, the hypertrophy may develop from chronic myocarditis due to increased work consequent on interference with the symmetric and orderly contraction of the chambers in this lesion.

Thus we see that the inability of the heart to bear increased strain, or the condition known as cardiac decompensation, may develop suddenly or gradually. With the clinical picture of the latter we are most familiar, as seen in chronic valvular disease, and the majority of cases of chronic myocarditis, but it is to the more rare group of those cases of suddenly developing cardiac decompensation in the subjects of chronic myocarditis that we desire especially to draw attention, which apparently have not been accorded, to date, sufficient consideration in the literature.

In this group we have a chronic myocarditis which has resulted in the majority of cases from the increased intracardiac pressure of arterial hypertension, in the minority of the subjects, from various degrees of obstruction of the coronary vessels. It is in this latter group of cases that the cardiac hypertrophy may result from the chronic myocarditis.

The most characteristic feature of this group of cases is that the attacks of decompensation are essentially and constantly intermittent. Between the attacks the individual may display no evidence of cardiac decompensation, has no dyspnea with ordinary effort, never develops edema; in a word, is able to go along through life in comfort; when suddenly, however, as a result frequently of some unusual efforts, some indiscretion in

diet, or a sudden rise in blood-pressure, or any shock or other cause that may disturb the balance of cardiac compensation, the victim is seized, most frequently during sleep, in the early morning hours, with a most severe dyspnea progressing rapidly to cyanosis, and ending in orthropnea with cold clammy sweat, pulse usually rapid, often weak, at times imperceptible. Cough, with bloody, frothy expectoration, frequently copious, with numerous bubbling crackling râles over bases of lungs, posteriorly especially; all of which pulmonary symptoms being due to resulting pulmonary edema. A general edema practically never occurs. Thus may be presented with astonishing rapidity in many cases the typical picture of circulatory collapse with sense and appearance of impending dissolution. A fatal result is, indeed, probable unless prompt medical aid be available, for very rarely is the heart able under such conditions to rally without rapid and energetic assistance.

The occurrence of pulmonary edema under conditions as before described is thus explained by Welch as quoted by Osler in his Practice of Medicine, chapter on Pulmonary Edema, where we read: "The theory most generally accepted (of pulmonary edema) is that of Welch, whose experiments seemed to indicate that pulmonary edema is due to a disproportionate weakness of the left ventricle, so that the blood accumulates in the lung capillaries until transudation occurs, such weakness may be brought about by paralysis or spasm of the left ventricle." Such a condition of affairs practically always obtains in attacks of acute intermittent cardiac decompensation. For in the more frequent group where we have arterial hypertension the circulatory collapse must in all probability be due to left ventricular paralysis from the strain of the intraventricular heightened pressure, while in the less common class, with no elevation of arterial pressure, but with rather constant accompanying symptoms of angina pectoris, consequent on coronary disease, spasm of the left ventricular muscle is the more probable cause of the acute circulatory failure.

In a series of 25 cases of which we have kept notes the following observations appear noteworthy:

Age.—All cases developed about the age of onset of arteriosclerosis and arterial hypertension, the youngest being forty years, the oldest eighty-three years.

Sex.—Incidence about the same in the two sexes.

Cause of Cardiac Weakness.—Arterial hypertension in a large majority of the cases, while coronary disease without arterial hypertension was seen in the minority of the subjects. Exciting cause of attack was some unusual physical effort or indiscretion in diet in the majority of cases. The attack did not follow immediately after the occurrence of the exciting cause, but usually several hours later, and frequently, as stated, during early morning hours.

Duration of Attack.—From one hour to three or four hours, rarely longer.

Recovery from Attack.—This is the most astonishing feature in this class of cases; just as it is so remarkable for one in apparent health to be suddenly found at times practically in the throes of death in this disease, so it is just as astonishing to witness this same individual in the space of a few hours emerge from a moribund state to one of almost complete comfort, clamoring to be allowed at least limited freedom once more, and to remain thus apparently well for a shorter or longer period until the next attack.

Intervals Between Attacks.—These varied between a few days in rare cases to several days, several weeks, and several months in other subjects, the average being four to six seizures annually. Some cases had several attacks at short intervals at onset of malady, and then went a number of months without any return of trouble.

Duration of Life.—A fatal result in first attack was not observed.

Case I.—G. W. D., aged sixty years, female (Fig. 55), seen September 27, 1916, well today, with no severe attack since above date, which was her first attack.

Case II. N. O. C., female, aged fifty-one (Figs. 56, 57), seen December 8, 1916. Well and working today, with no severe attack since October 22, 1920.

Case III.—J. M. W., female, aged sixty-five years (Fig. 54), seen first June 22, 1916. Living and comfortable today. No severe attack since June 22, 1921.

Case IV.—A. J. S., male, aged forty-eight years (Fig. 60). Well and in active business today. No attack since one coming

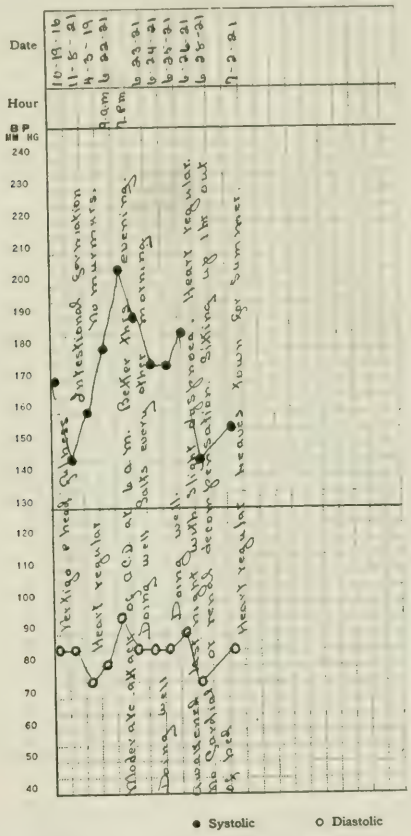

Fig. 54.—J. M. W., female, sixty-five years. Living and well six years after first attack. Hypertension moderate. No anginal symptoms.

under observation June 24, 1919. Anginal symptoms marked during attack.

E. K., male, seventy years, under observation since February 11, 1916. Blood-pressure constantly low. First attack

May 30, 1921. Well and working today. No repetition of attack since.

G. C. R., male, seventy-five years, came under observation January 8, 1915. Case changed to one of chronic cardiac de-

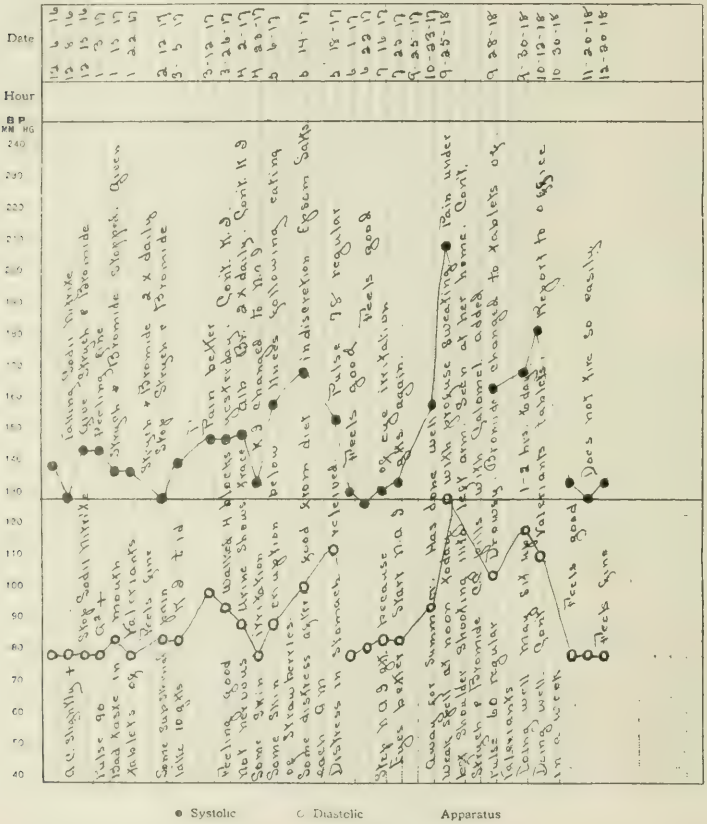

Fig. 55.—G. W. D., female, sixty years. Well today, six years after first attack, September 27, 1916. Hypertension very slight. Element of angina pectoris marked.

compensation about February 21, 1921. Patient died March 18, 1921.

J. B., female, sixty-eight years (Fig. 58), came under observation January 2, 1917. Died about one year later in an attack of acute cardiac decompensation.

I. C. S., female, seventy-two years, died August 30, 1908, four years after first attack, weathering four to five attacks annually, three of them so severe as to cause difficulty at climax of paroxysm in determination of presence of life. Finally

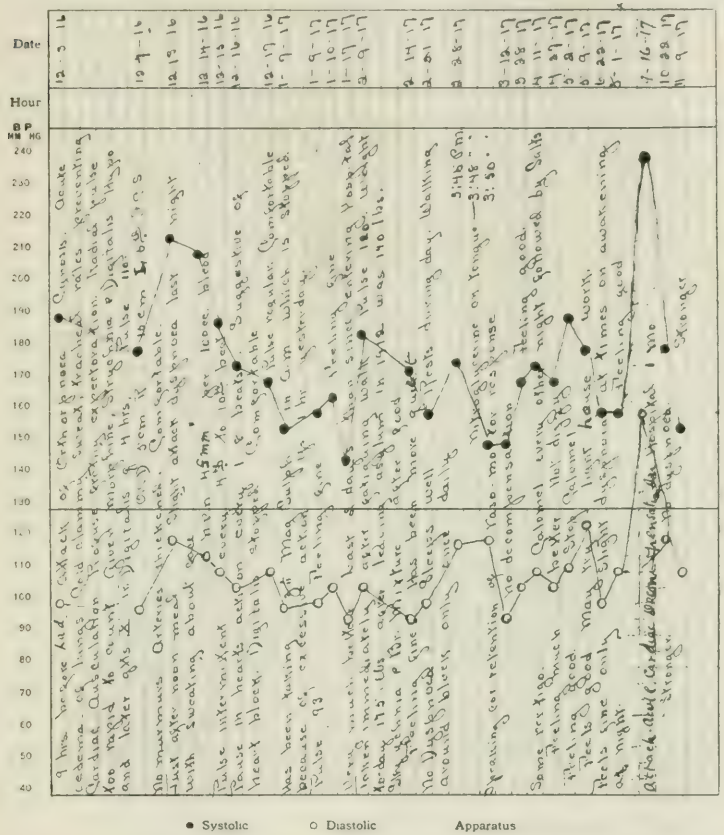

Fig. 56.—N. O'C., female, fifty-one years; well and comfortable today. First attack December 8, 1916. Last attack October 22, 1920. Note extreme hypertension with attacks.

expired in an attack following overexertion day preceding death. Always active and cheerful between attacks.

Prognosis.—The cases cited, though few and brief, are nevertheless quite suggestive as to life expectancy in these cases. In the first place, if efficient medical aid is available promptly

in a first attack the outlook for recovery from the attack is fairly good. With each subsequent attack the prospect of recovery, of course, grows less, though as the case reports show, an individual may survive repeated attacks for from four to

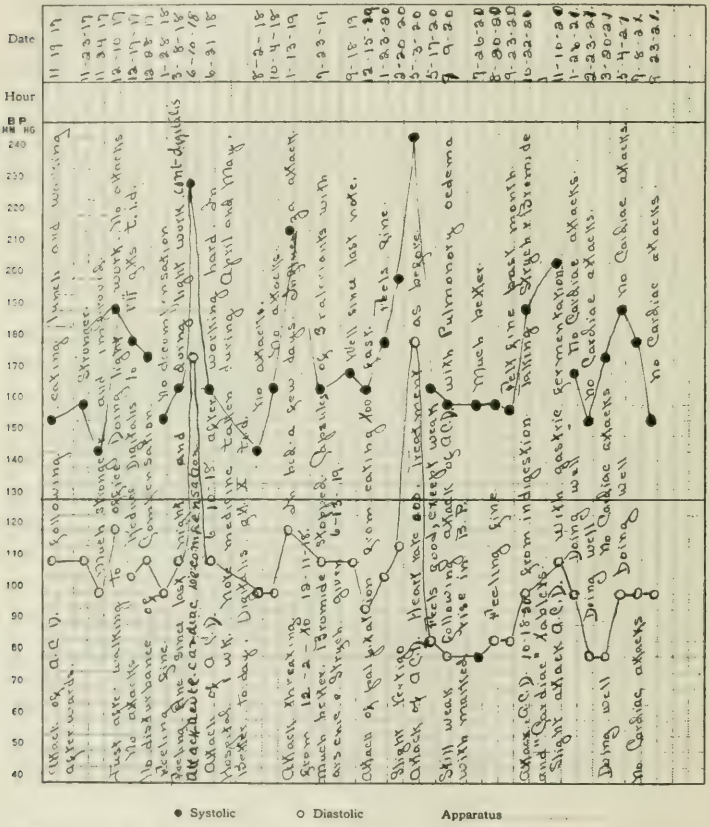

Fig. 57.—N. O'C., female, fifty-one years; well and comfortable today. First attack December 8, 1916. Last attack October 22, 1920. Note extreme hypertension with attacks.

six years. The family, however, should always be apprized of the fact that the sword of Damocles overhangs anyone the victim of acute intermittent cardiac decompensation.

Treatment of this group of cases should be divided into the treatment of the attack and the management of the cases

in the intervals from the standpoint of prophylaxis. Treatment of attack should be further divided into: (*a*) those with arterial hypertension and (*b*) those *not* so complicated.

(*a*) Blood-pressure should always be determined by the sphygmomanometer unless the condition of the patient be too

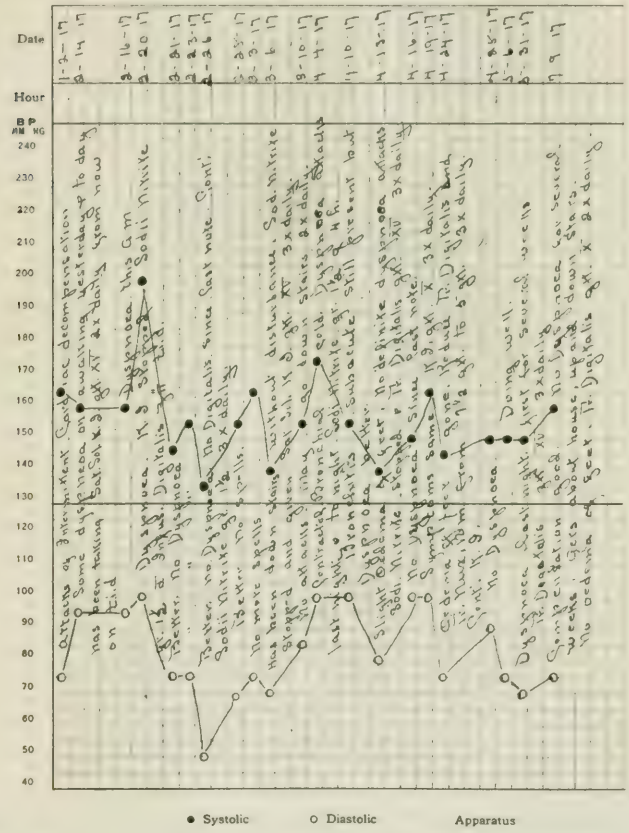

Fig. 58.—J. B., female, sixty-eight years. First attack January 2, 1917. Died one year later in an attack of acute cardiac dilatation. Patient most uncomfortable when blood-pressure was highest.

critical to permit of such delay, when blood-pressure should be approximately estimated by character of pulse, as element of time is so all important in rescuing these patients from the jaws of death. Hypertension having been determined, $\frac{1}{50}$ grain

of nitroglycerin should at once be given hypodermically, and repeated every fifteen to thirty minutes, as indicated by blood-pressure readings (cuff of instrument being left on arm); $\frac{1}{2}\frac{1}{5}$ grain of reliable digitalin should also at once be injected and repeated

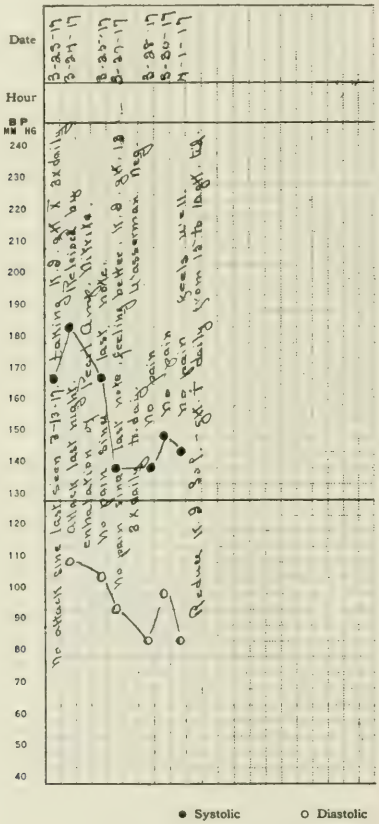

Fig. 59.—D. F., age seventy years. Seen first March 27, 1917. Died about one year later in an attack of angina pectoris. Tracing shows a moderate hypertension with very severe attacks of angina pectoris. The involutionary type of arteriosclerosis.

in one-half to one hour as required; $\frac{1}{2}\frac{1}{0}$ to $\frac{1}{3}\frac{1}{0}$ grains of strychnin sulphate hypodermically, repeated as indicated, is also called for.

To control the demoralized state of the patient's mind, and especially should there be any anginal symptoms, $\frac{1}{4}$ grain

of morphin is to be injected combined with $\frac{1}{150}$ to $\frac{1}{100}$ grain of atropin sulphate, which latter is urgently needed for any element of collapse. Both to be repeated as indicated. An ampule of camphor hypodermically is also to be administered

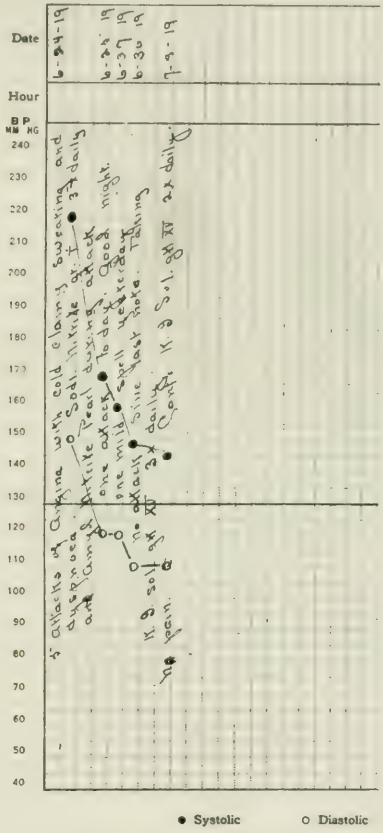

Fig. 60.—A. J. S., male, forty-eight years. Well and active in business since attacks on June 24–26, 1919. Note several attacks at onset—none since. Also high blood-pressure, with marked anginal symptoms, a rather unusual combination.

every fifteen minutes until patient rallies. For cyanosis oxygen should be freely and constantly administered until cyanosis shows signs of disappearing. The patient should not be allowed to make any special effort to inhale the gas, but the tube

should be held near the mouth or nose that the oxygen may enter with the inspired air.

It is comforting to witness that from this plan of treatment promptly administered a good proportion of these cases will

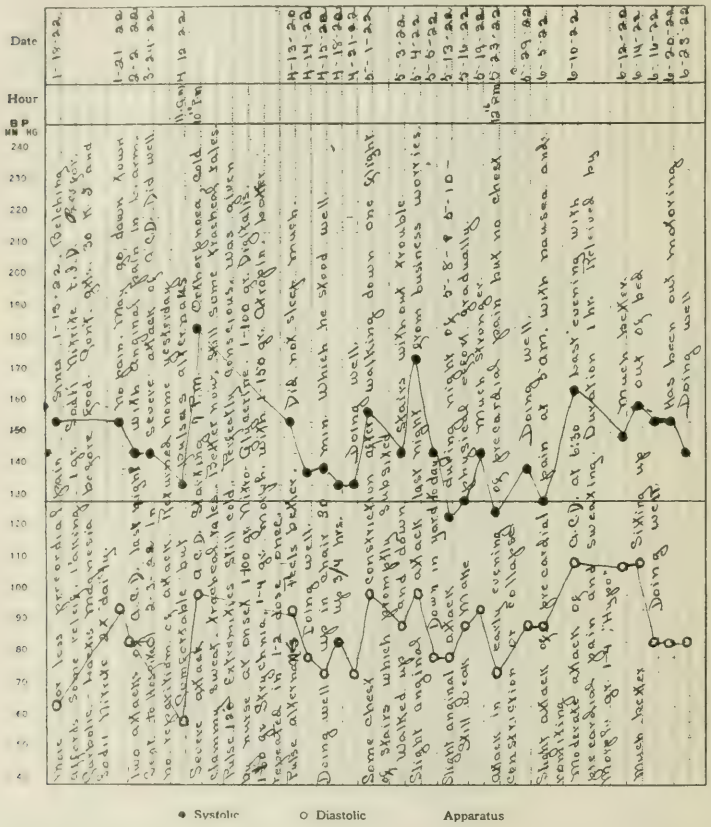

Fig. 61.—W. K., male, fifty-five years. Under observation since January 13, 1922. Still at hospital, doing well now, but attacks easily precipitated by any undue excitement, exertion, or indiscretion in diet.

in a comparatively brief space recover from their most precarious condition, and no matter how hopeless the victim may at first appear, faithful, persistent efforts will sometimes bring successful results. We should work with such a case as persistently and as long as we would in a case of drowning, for

instance, as we have seen at least 2 cases come out of such attacks, when, to all intents and purposes, they seemed moribund.

In those without arterial hypertension the treatment is practically the same, with the exception of omitting vasodilator drugs, such as the nitroglycerin, which, of course, are not indicated. In this class of cases the so-called involutionary type of arteriosclerosis is present in contradistinction to the hypertensive variety, and there being, as a rule, more marked involvement of the coronary vessels, the symptoms of angina pectoris tend to dominate the picture, calling for more free use of morphin. With the above exceptions the therapeutic indications remain the same in these two varieties of cases.

When our remedial efforts in such seizures meet with success the management of the case then becomes that of the patient in the interval of attacks.

Having treated a patient through one of these most dangerous of maladies, and appreciating the great importance of prompt medical aid, provision should at once be made to have the remedies administered at onset of symptoms before the arrival of the physician, and, in the absence of a trained nurse, some member of the family or a friend should be shown how to administer the hypodermic injections of the medicines which should be constantly kept on hand in tablet form, plainly and properly labeled.

In the interval management of this disease it is also most important to determine the presence or absence of arterial hypertension, for not only does the treatment vary in the two groups, but it requires only a glance at the accompanying charts to realize what an all-important rôle hypertension plays in the group with high blood-pressure in precipitating the recurrence of attacks; for with every attack we see on the charts a definite rise in blood-pressure, and it has been our experience that if the hypertension can be kept under control the patient remains free of attacks, if not indiscrete in other ways. The control of tendency to arterial hypertension, of course, involves several basic therapeutic principles—coffee, tea, and nicotin should be

stopped at once. Alcohol may be allowed in moderation to those accustomed to its use and to the feeble, provided there is no serious grade of nephritis.

When the non-protein blood nitrogen is excessive a low protein diet must be faithfully adhered to, and even more rigidly, should defective renal elimination be manifested by a low phenolsulphothalein reaction.

Should the non-protein blood nitrogen not be high, then careful search should be made for any focal infections in teeth, tonsils, nasal sinuses, gall-bladder, appendix, and organs of generation, with their radical removal whenever found.

Free elimination is also indicated through, first, skin. By frequent bathing, with friction and care of skin, and during cold weather sweat baths; second, through bowels. Here we should procure not only cleansing of bowels through saline laxatives but also thorough cleaning of portal circuit with so-called cholagogue remedies, as calomel, podophyllin, colocynth, etc., as very effectively combined in the compound cathartic pill improved or unimproved. A good plan is to give Epsom salts in the morning, with calomel or cathartic pills the same night, omitting all purgatives next day, but repeating these remedies every other day. In this way we have bowel movements from the salts on the day they are given, and stools the day following from the cholagogue remedies; should results become excessive, two, three, or four days may intervene between the administration of the purgatives, the administration of the vasodilator drugs being kept in reserve for the attacks, or continued over shorter or longer periods when there may be a tendency to repetition of attacks at short intervals with high blood-pressure as a cause, or when the hypertension proves very intractable to above enumerated general principles of treatment. For administration over more or less extended periods of treatment the nitrite of sodium in doses of 1 to 3 grains, or the erythrol tetranitrate in $\frac{1}{2}$-grain doses, both given three times daily, are preferable.

The saturated solution of iodid of potassium or sodium in 10- to 20-drop doses, well diluted, is also indicated in prolonged

and intractable cases. The bromids are also helpful when there is a large nervous element.

In the group without arterial hypertension the involutionary type of arteriosclerosis is behind the coronary artery disease and the chronic myocarditis, and as this appears to be largely a congenital affair, appeal here shall have to be made to eugenics. Some, however, believe that excessive intake of chlorid of sodium may here be an etiologic factor and should, therefore, be controlled. Lues, of course, should always be looked for, and it is in this class especially that the iodids of potassium and sodium are indicated, especially for the control of the complication of angina pectoris so frequent in this class of cases. As general prophylactic measures both groups of this malady should be strongly warned against any undue physical effort and also any indiscretions in diet and venery.

In conclusion we desire to summarize:

1. Acute intermittent cardiac decompensation is a well-defined clinical entity which deserves more attention than is generally accorded it in the literature.

2. Arterial hypertension is a most important factor in determining the attacks and in causing the fatal termination through excessive cardiac strain.

3. Control of arterial hypertension affords most valuable prophylactic and therapeutic results.

4. Prognosis need not necessarily be considered too grave, for even in apparently hopeless cases recovery from the attack may occur when prompt and efficient medical aid is available.

CLINIC OF DR. LLEWELLYN SALE

Jewish Hospital

TUMORS OF THE MEDIASTINUM: 3 CASES

I shall show you one case and briefly recount the course of two others. Each one of these cases shows a lesion of the mediastinum, and from each one a lesson may be learned.

Mr. B., Medical No. 24,176, was admitted from the dispensary on May 31, 1922. He came there complaining of difficulty in swallowing and loss of weight. A tentative diagnosis of carcinoma of the esophagus was made by me in the out-patient department, and the patient urged to go to the hospital. Here we learned that symptoms first showed themselves nine months ago. At that time some slight difficulty in swallowing was first noticed. Solid food at times seemed to stick, and several swallowing efforts were required to force it down. Gradually this difficulty grew worse and now he cannot get down solid food at all. Often he eats something that lodges in his esophagus and is very shortly regurgitated. Liquids and semisolids he was able to manage quite well when he came in, not as well as you or I, but they did go down. His past history and family history tell us nothing that can have any bearing on his present condition. He told us that he had lost 90 pounds in nine months (weight on admission 146 pounds) and he had grown very weak. He complained, then, of difficulty in swallowing, progressive weakness, and also of a pain between the shoulders that kept him awake at night and that was sticking in character. On admission he looked like a weak, emaciated old man. He was somewhat pale. His pupils were unequal, the right larger than the left. They were regular in outline and reacted promptly to light. Teeth and gums in poor condition; tongue furred; fetor

exore. Pharynx negative. Few small cervical glands. Chest resonance good, respiratory murmur normal, no râles. Heart 11 cm. to left, 5 cm. to right of midsternal line. Irregular pulse of the bigeminal type. No wide area of dulness behind upper sternum; no dilatation of veins of chest wall. Arteries hard. Abdomen scaphoid, wall thin, and in folds. No mass palpable; no tenderness. Prostate not large. Extremities negative. Fifteen years ago, when I was an intern, we would at this point have introduced esophageal sounds in order to accurately locate the obstruction, to determine its size, and to stretch it. An ingenious sound, devised by Schreiber, I believe, had a metal rod and tip at the distal end. The rod was very supple and imparted to the hand of the manipulator different sensations that varied with the nature of the tissue over which the tip passed. If the obstruction was benign, the tip glided along smoothly; if malignant, a coarse, jerky movement resulted. Such an instrument has its place today in a collection whose interest is only historic. Our patient was referred to the *x*-ray department, where he was studied by Dr. Schnoebelen and his able assistant, Miss Appel. Their reports are, as you see, quite voluminous, and I shall try to condense them for you. The barium mixture, as it descends, is definitely retarded at about the level of the second intercostal space. Above this there is a dilatation whose outline is smooth. The constriction is not complete. Stomach and duodenum negative. The *x*-ray film shows a triangular-shaped barium shadow, apex at the level of the bifurcation of trachea, base up. In other words, the *x*-ray shows that the lumen of the esophagus is much narrowed, and that this narrowing is most marked at the level of the tracheal bifurcation. There is nothing to be learned from this examination as to the nature of the obstructing lesion. It is located at one of the sites at which carcinoma often occurs. The man is sixty-three years old, he has lost much weight, and become quite weak, and, most important of all considerations, is the fact that an obstruction of the esophagus, when due to intra-esophageal lesion, is usually malignant. It will be valuable for you to remember this fact. You remember that the patient had pupils that were unequal

in size. I do not know how often unequal pupils are due to syphilis; a comprehensive statistical study on this question would be interesting. Unequal pupils are always useful if they make you think of syphilis in any case in which you find them. This patient's blood Wassermann is negative. His urine shows no marked changes, his blood a mild secondary anemia. His stools contain occult blood, a frequent finding in malignant disease of the gastro-intestinal tract. Antisyphilitic treatment was instituted. In these cases, in which I feel very strongly that syphilis is not a factor, but in which I cannot be sure of that fact, I give my patients mercury and iodid by mouth. The patient began to improve shortly after his admission, and this improvement was due, I am sure, to careful regulation of his diet. He was given liquid and soft foods that could pass through and that did not irritate his esophageal mucous membrane. His pain in the back continued. In a vague sort of way I attributed this to pressure; its exact mechanism I do not understand. Shortly after he came in two unsuccessful attempts were made to look into his esophagus. On June 24th one of our laryngologists succeeded in esophagoscopy. His report reads as follows: "Tube passed as far as mouth of esophagus. Here was seen a mass protruding from the right; appearance of myxofibromatous tissue. From the left there protruded a mass which had the appearance of edematous mucosa. Anteriorly could be plainly seen the lumen of the esophagus so small as to preclude the possibility of passing even a small tube without injury. A piece of the right mass was removed for examination." The laryngologist assured me that the growth looked like carcinoma. Here, then, was a new development. A carcinoma higher up than the one that was causing the obstruction. Papillomata are not infrequent in the esophagus, and have been reported several times in cases in which there was also a cancer. But this growth did not look like a papilloma. The small piece was removed and the pathologist reports squamous-cell carcinoma. Following the esophagoscopy our patient could not swallow even liquids. He had had no fever up to this time, but on the evening of the day that he was esophagoscoped his

temperature went up to 102.4° F. Since then his temperature has been up every evening—101° to 103° F. Water was given to him under the skin and by rectum, in the hope that the closing up was the result of trauma and that we could soon feed him as before. I believe that during the esophagoscopy and excision considerable damage was done to the wall of the gullet and an infection at the site resulted. We waited a week for the complete closure to improve, but as it did not do so, and as the patient grew progressively weaker, a gastrostomy was neatly done by Dr. Max W. Myer, and a tube introduced through which the patient was to be fed. We have been putting liquids in, but he is still too weak to attempt to chew food himself and then have it put into his stomach. On June 20th he was given deep *x*-ray therapy, and if he survives, this will be repeated. Eight or ten years ago Oppenheim, the well-known neurologist, in a thoughtful paper, warned us of the dangers connected with lumbar puncture, and insisted that our chief concern should be that in our examinations we must be very careful to see that as a result of them no harm comes to our patients. Medicine has advanced much in the last few years, and this warning, timely then, is today never to be forgotten. It was proper to esophagoscope this patient, and I know that the operation was done by an expert. I feel, nevertheless, that his present condition, from which I do not expect him to rally, resulted from this examination. I hope that my pessimism is unwarranted and that I shall be able to show him to you again in a few weeks much improved.

The case whose history I shall now review some of you have seen. He died a few days ago. I was asked to see him in consultation by Dr. J. C. Kopelowitz. He was about forty years old and had had fever for about three weeks. The onset was characterized by malaise and cough, but he stayed at his work (traveling salesman) for some time. His physician, at the first examination, found signs of consolidation at the left base, which he interpreted as a resolving bronchopneumonia. A week later his whole left side was flat on percussion, and Dr. Kopelowitz

sent him to the hospital. At this time I saw him, and he presented the signs of a massive solidification of the left lung—flat percussion note, bronchial breathing, and loud transmission of the spoken voice. You must learn at some time, and you may as well do so now, that these classical signs of a solid lung may be, in fact often are, due to fluid. Anyone who went through the empyema epidemic in our camp hospitals learned this lesson. The old dictum that "fluid does not transmit sound" was never good physics, although when I was a student it was always offered as the explanation for diminished or absent breathing and voice over a pleural exudate. Whenever you elicit a dull note over a considerable area in the chest think of the presence of fluid as its cause, no matter what the auscultatory signs. If the note is flat, you may confidently expect to get fluid. Screen your patient if you can, and then aspirate. Use a little novocain for local anesthesia; use a sharp needle of fairly large caliber. Do not wiggle your needle; you may traumatize the lung. If you get a dry tap and want to try again, withdraw your needle, sterilize or take another, and repeat at another site. We made an exploratory puncture and got a serosanguineous fluid. Later we withdrew 3 liters. At this time our patient had no fever, but much cough and great dyspnea. It is remarkable how little respiratory distress a massive pleural exudate may cause, but we thought our patient had a bronchopneumonia and that his dyspnea was due to this. Our reasoning was faulty. We had emptied the pleural cavity pretty well, for an *x*-ray now showed very little fluid, but a huge heart-shaped shadow in the left chest, extending on the left to the chest wall, well to the right of the median line, and very wide at the base. The *x*-ray diagnosis was pericardial effusion, and we accepted it. In each axilla was a gland as large as a walnut, a finding to which we did not at first pay sufficient attention. Leukocytes on admission were 12,000; Hb. (Sahli) 85 per cent.; red cells 5,000,000; differential formula normal. Aspiration of the pleural fluid in no measure relieved the patient. His dyspnea became an orthopnea and was never improved. The chest fluid showed blood and a preponderance of mononuclear cells, not endothelial. No organ-

isms were found in smears. On one occasion the laboratory reported a Friedländer bacillus, and this helped to confuse us. Guinea-pig remained well after inoculation. On nine different occasions we attempted to withdraw fluid from the pericardium. You will find when you look this subject up that many different sites of election have been described for pericardial aspiration. This means that there is no site of election. Go in over the fluid area and avoid, as far as you can, injury to important structures. You may be called upon more or less often to attempt to aspirate pericardial fluid, and whenever you do so you will do it with fear and trembling if you are human. At one aspiration the needle oscillated with the heart-beat and we felt that the 300 c.c. of fluid that we got came from the pericardium. It resembled in every respect the liquid I have already described. Dr. Evarts Graham saw the patient to help us determine whether or not surgical interference was wise. He advised further attempts at aspiration. The patient's condition grew more deplorable daily. He could now breathe only when he was leaning forward and to the left, supporting himself on a chair or table. His cough became brassy, his voice husky, cyanosis deepened, he could not sleep, and he became very apprehensive. The possibility of a mediastinal tumor as the cause of his difficulty had suggested itself, and on April 1st, four weeks after I first saw him, the conclusion that this was the correct diagnosis seemed unavoidable. A mediastinal exploration was now decided to offer the only hope. The tumor might be removable. At any rate, Dr. Graham felt that decompression might bring subjective relief unless the mass encircled the trachea. On April 3d, under novocain, he split the sternum and exposed the growth. The technical difficulties were very great. The patient was almost *in extremis* and could only sit with his trunk bent forward. He died just after the sternum had been divided. The tumor was now seen to be a huge mass that surrounded the heart, hilus, vessels, and trachea. There was no pericardium, just a thick mass of neoplastic tissue surrounding the heart. A piece of the mass was excised and one of the axillary nodes removed. These were submitted to the patholo-

gist, who returned a diagnosis of lymphosarcoma. Let me briefly review the salient features. The disease began with fever, cough, and malaise at a time when grip was prevalent. A pleural effusion from which the laboratory recovered a Friedländer (?) was looked upon as an inflammatory exudate. Its serosanguineous character was not carefully enough considered. An *x*-ray diagnosis of pericarditis with effusion was too readily accepted. Absence of fever (shortly after the onset) and toxic symptoms, disproportionately marked dyspnea, enlarged axillary glands, and failure to get fluid from the pericardium were not given sufficient weight by us in our consideration of the case. An earlier correct diagnosis would have influenced our prognosis only. I do not believe that *x*-ray or radium could have accomplished anything.

Finally I shall report the end-result of a case which I showed you several weeks ago. Let me briefly recall it to you. A young woman, aged twenty-six, who had had gradually increasing difficulty in swallowing for three months. When we saw her together she could not swallow anything but liquids and was very weak and undernourished. You remember that the *x*-ray showed that the column of barium was arrested in its course at the gastric end of the esophagus, and that the lumen of the esophagus was dilated above this point. We passed an olivary tipped bougie, and some of you remember how firmly it was held after once engaged in the stricture. The blood at that time showed no deviation from the normal. The Wassermann test was negative. We made a diagnosis of carcinoma of the esophagus and referred her to a clinic that has radium at its disposal, and that has been treating cases of this character with success. There the *x*-ray examination was repeated, and a diagnosis of cardiospasm resulting in esophageal obstruction and dilatation was made. The outline of the esophagus was smooth, not rough and ragged, and this, I believe, made them feel that the obstruction was benign, and not, as we had thought, malignant. Radium was, of course, not used, but it was decided to dilate the stricture. On May 16th, while a bougie was being passed,

the patient complained of great pain and went into a state of shock. She was given morphin and sent home. Later in the day a physician sent her to this hospital. On admission she was pale, cold, and clammy; temperature 100° F.; pulse 140; leukocytes 19,000. She complained of severe epigastric pain and had an anxious expression. She was breathing rapidly and percussion note over left lower chest was dull, and over this area breath sounds and voice transmission were diminished. When the lower end of the sternum was percussed she complained of pain. Abdomen was distended and tympanitic and there was muscle rigidity in epigastrium and right upper quadrant. A diagnosis of perforation of the esophagus was made. She ran a septic course, vomited foul-smelling, bloody material, and continued to suffer and to grow weaker. Percussion dulness was soon present posteriorly on both sides, with distant breath sounds and bubbling râles, and it was evident that she had a septic pneumonia. Six days after admission she died. Autopsy showed a purulent effusion in right chest, a bronchopneumonia, a suppurative mediastinitis, a carcinoma of the gastric end of the esophagus, and a perforation of the same. The outstanding lesson to be learned from this case is that the *x*-ray is but an adjunct to diagnosis. The clinical history and the physical findings have not been relegated to the rear; their importance has not been diminished one jot or tittle. When I was a student our teacher, the late lamented Jesse S. Myer, insisted that every esophageal obstruction was to be considered malignant until it could be definitely proved benign. I remember with what frankness he reported cases that he had considered functional cardiospasm that were later found to be esophageal cancers. I commend to you his paper on cardiospasm, which appeared in the Journal of the American Medical Association about twelve years ago.

CLINIC OF DR. RALPH A. KINSELLA

From the Medical Clinic, Barnes Hospital, Washington University School of Medicine

A BACTERIOLOGIC CLINIC—DIAGNOSTIC METHODS

In the preceding clinic we discussed the symptoms of infection and endeavored to analyze the features which distinguish the fever of infection, for example, from fever of non-bacterial origin. We pointed out that a purely non-bacterial disease, such as serum sickness, or the reaction following the prophylactic injection of typhoid vaccine, may even produce a continuous fever which renders it difficult to separate, by this symptom alone, an infectious from a non-infectious fever.

Modern laboratory methods have in many cases provided the means by which we may advance in the diagnosis of fever and the blood-culture, the serum tests—such as agglutination and complement fixation—are aids whose usefulness and limitations are, I think, strikingly displayed by the study of the cases to be presented today. Such cases have been selected as emphasize the ease with which laboratory methods establish a diagnosis in some cases and the failure of the same methods in other cases. This latter type of case is more important. Much discussion is still heard concerning the value of laboratory tests in the diagnosis of certain infections. Often a clinical diagnosis is stubbornly maintained in the face of a negative and reliable test, and the understanding of infectious processes is often weakened by giving too much emphasis to an isolated and trivial laboratory test even though reliably performed. The light which is thrown on this disputed ground by the study of the following cases would strengthen our position and make us more certain of our conclusions in such matters in the future.

Case I.—Male, thirty-two, white, married salesman.

"*Chief Complaint.*—Fever, weakness.

"*Onset* very gradual while working in rural district. Illness began with feelings of fatigue and lassitude. Then headache and backache followed, and there was an occasional chill in first week of illness. The patient was ill for two weeks before entering hospital."

Here we have the description of the attack by some infectious agent, which has maintained its activity in the patient's body. What part of the body?

"*Additional Symptoms.*—There is an occasional cough, with white mucoid sputum. There is a slight feeling of tenderness in the abdomen, and the habitual posture of the patient in bed emphasizes this feature inasmuch as the hands are always laid upon the chest and not on the abdomen. Stools are more frequent than normal.

"Examination reveals a definite diffuse reddening of the pharynx and tonsils; a reddened tongue, coated in the middle; occasional coarse râles on both sides of the chest; regular heart action free from murmurs and without enlargement of cardiac outline; dicrotic pulse; a soft, doughy abdomen; palpable soft spleen; and numerous pink macules some of which seem slightly raised, which are scattered over the abdomen and, to a much less extent, over the chest, arms, and thighs. The stools are loose." This is the description of a diffuse infection which has perhaps found localization in the skin, the lungs, and intestines. We are in the habit of calling such a disease typhoid fever, but without laboratory proof we stand in the position of the clinician who saw such cases before the birth of bacteriology. Such a case is one of enteric fever.

"*Laboratory Data.*—Leukocytes 4000; urinalysis negative; Wassermann negative; Widal negative; blood-culture positive."

The statement is often made that the blood-culture is often positive early, the Widal late. It must be remembered that there is often a positive blood-culture as late as the twenty-fifth day in the presence of an agglutination reaction positive in a 1 : 1200 dilution of patient's serum.

In this case, although several positive blood-cultures were obtained, the Widal reaction never became positive. Before the patient left the hospital three negative stool and urine cultures were obtained, indicating to a reasonable degree of certainty that typhoid bacilli were no longer present in the gastro-intestinal or genito-urinary tracts. But just after leaving the hospital this patient developed signs of phlebitis in the left saphenous vein. We have no record of a blood-culture taken during this phlebitis. The patient returned to the hospital three weeks later with a positive blood-culture (Bacillus typhosus) and suffered a relapse which lasted thirty-six days. This would indicate a hematogenous mode of invasion which must be regarded as unusual.

Case II.—This is a type of case similar to the preceding one in the certainty with which the laboratory examination establishes the diagnosis. This is a white male, forty-three, married, shoe factory worker.

"*Chief Complaint.*—Chills and fever with backache for two weeks.

"*Onset.*—Severe pain in back of head and neck announced the illness. This was sudden in appearance and was followed in a few hours by a chill, which lasted a few minutes. These chills and headaches have occurred daily for two weeks, and during the past week there have been pains in the shoulders, wrists, and knees. Fever has been present every day."

Here again is the description of the attack made upon the body by some infectious agent. Where is the seat of its activity?

"*Other Symptoms.*—Weakness has been noticed by patient for past six months, but of an indefinite nature. Coughing and expectoration have been present for several months. There has been an occasional precordial pain with vomiting and palpitation."

This creates the impression of chronicity, and the doctor who saw this case first thought the patient might be suffering from pulmonary tuberculosis, chronic infectious arthritis, malaria, or perhaps neurasthenia.

"*Examination.*—Dull, apathetic; eyes bright and glassy; no apparent discomfort; sensorium clear; no edema or dyspnea; no eruption or jaundice. Teeth show many fillings and much caries. Gums red and swollen; tonsils enlarged and red; tongue heavily coated.

"Chest shows prominent clavicular fossa. Resonance slightly impaired throughout and there were coarse râles on both sides. The left border of the heart was extended on percussion, and there was a diastolic murmur at the aortic area, with a blood-pressure of 120/55, and definite capillary pulse. Spleen not felt. No signs of arthritis." Here, then, is the picture of an infection the duration of which is indefinite, and the most evident focus of this infection is associated with the aortic valve. The occurrence of rheumatic pains without evident arthritis might lead us to think of this as an old case of rheumatic fever with fresh inflammation of various joints. The febrile feature, while speaking for infection, does not tell us that this is a case of bacterial endocarditis. Such a picture may exist without bacteriemia, and subsequent autopsy reveals a non-bacterial vegetation. Let us consider the laboratory data.

"Wassermann reaction negative; tuberculosis complement fixation ++; *x*-ray of chest led the roentgenologist to offer a diagnosis of pulmonary tuberculosis.

Cultures: Blood: Streptococcus viridans positive for three weeks, after which patient left the hospital.

Sputum: Hemolytic streptococcus.

Each of these laboratory results is interesting and suggests comment.

The negative Wassermann recalls how frequently the aortic valve is diseased in non-syphilitic infections. We have previously emphasized the statement that the accuracy of any Wassermann technic must be criticized in the light of the agreement of the test with the clinical diagnosis. Much of the distrust of the laboratory on the part of some clinicians and much of the dogmatic positiveness on the part of some laboratory workers could be obviated if more attention was paid to this point. The day's work in the laboratory should always be

studied in connection with clinical diagnoses, and the latter should always be given to the laboratory.

We have been impressed with the usefulness of the tuberculosis fixation test when positive. We have used the antigen and technic advised by Fleisher. In this case the positive test is impressive considered in connection with the *x*-ray findings in the lungs.

The nature of the infection is established, as it always must be in this type of case, by the blood-culture. Fifteen to 30 colonies per cubic centimeter of blood of the same streptococcus were always recovered in the three cultures that were made before the patient left the hospital. The diagnosis of bacterial endocarditis could not be made without such evidence. Such evidence is easily obtained. There is perhaps no variety of bacteria more easily cultivated than this type of streptococcus. The absence of a positive report should never lead to loss of confidence in the laboratory.

It will be recalled that the word "viridans" does not describe a particular streptococcus, but a family whose characteristic is the production of green on blood-agar plates. There are perhaps innumerable streptococci possessing this feature, and no two cases have ever been reported that were infected by the same member of this large family of streptococcus.

The foregoing is a consideration of cases in which the bacteriology is definite. More often we are confronted with cases whose clinical features are suggestive of infection, but must remain undetermined because laboratory methods either are inadequate to detect the organisms in the blood and other sources whence cultures are sought, or the specific organisms are not in the locality in which we seek them. There is no group of cases in which it is more difficult to speak definitely than the group of rheumatism infections which are not obviously bacterial and easily proved as such, as, for example, a gonorrheal joint.

Case III.—White, female, twenty-three, housewife.

"*Chief Complaint.*—Fever, prostration.

"*Onset and Course.*—Two weeks prior to admission patient

was delivered by a midwife and badly lacerated. Repair was immediately done, but infection of the wound followed. Patient became very sick, and the first doctor who saw her thought she had "puerperal sepsis." For this he administered antistreptococci horse-serum (four days after delivery), and within a few days the temperature was reduced and remained only slightly elevated until the twelfth day after delivery. Since then a profuse vaginal discharge of foul odor has been present, fever has been constant, and there has been tenderness in the lower abdomen. There have been no chills; no gastro-intestinal signs; no respiratory difficulty." We can readily assume that this is the description of general infection subsequent to wound inoculation. Physical examination confirmed this assumption. The character of the infection was established by the laboratory. A heavy growth of hemolytic streptococcus was obtained from the culture of the vaginal discharge.

Repeated blood-cultures were negative. Leukocytes 17,000.

The statement that this patient was well for three days after delivery is in striking correspondence with the incubation period of this infection as we understand it from experiments on laboratory animals. Then symptoms began. With proper treatment of the local source of infection symptoms subsided. We cannot feel that antistreptococcus serum has any specific usefulness, but this patient became sensitized to horse-serum, and the subsequent course in the hospital presents a remarkable series of events, and illustrates our difficulties and the shortcomings of laboratory tests in such a case.

"Twenty-seventh day after delivery: Patient has been complaining of pains in her joints for twelve hours. The pain is limited to shoulders, elbows, wrists, left knee, and temporomaxillary joints. In last three hours a rash of a scarlatiniform character has appeared over entire body. Throat is negative, there is no cough, and she has not received medicine recently. Fever has risen to 104° F.

Heart is negative and abdomen reveals no new signs. Measurements of joints: Left knee, 35 cm., right knee, 34 cm. in circumference.

Here is a case of polyarthritis which might well be suspected of being connected with the local infection from which hemolytic streptococci could still be cultivated. Blood-culture at this time was sterile. The patient said she had discovered a few "hives" on her body shortly after entering the hospital, and such a condition would be expected after the injection of horse-serum. We are equally affected in our reasoning by the remote source of serum sickness which would make the polyarthritis an anaphylactic display and the nearer hemolytic streptococcus infection which would lead us to regard the arthritis as a metastatic outbreak.

We are not helped by the laboratory in this case. The subsequent clinical course is better evidence. This patient was free from fever, from the eruption, and from all joint pains within forty-eight hours of the onset. Accordingly, we cannot feel that a hemolytic streptococcus which caused so violent an infection in the uterus would be so different in its behavior in the joints. Such transitory states are never associated with hemolytic streptococcus invasions. Hemolytic streptococcus in the joint cavity are virulent and cause purulent destructive inflammations.

Either this is a belated serum disease or a combination of effects caused by the streptococcus infection and the anaphylactic state.

These cases illustrate how our attitude toward bacteriologic diagnosis is influenced by laboratory data. They serve to show us the importance of such data and the difficulties of diagnosis when such data are absent.

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